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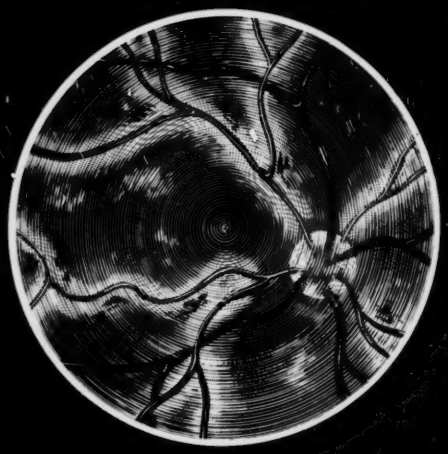

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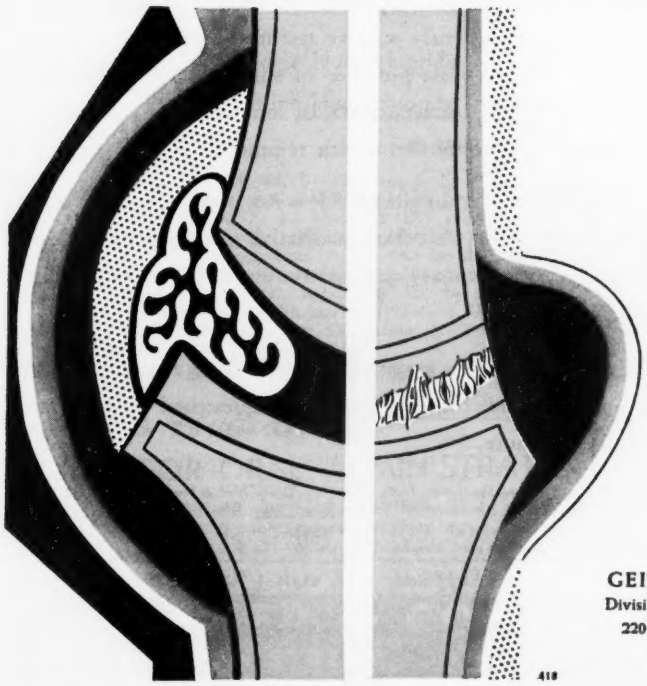

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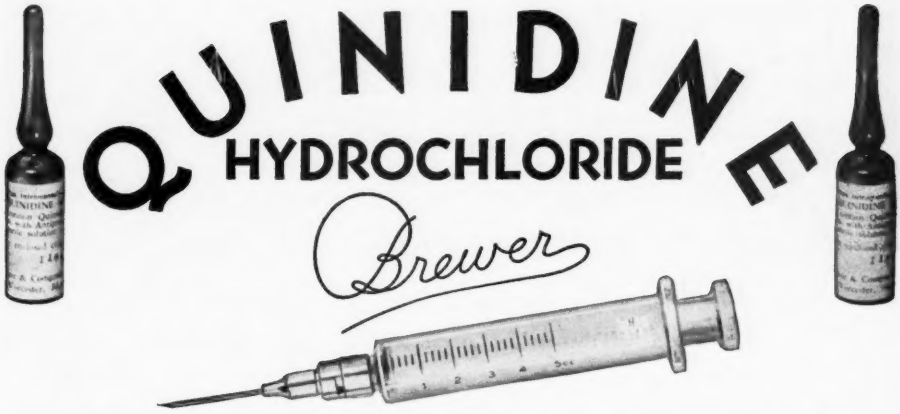

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1. Rev. Gastroenterology 20:744 (Oct.) 1953; abstract in J. A. M. A., 153:1580 (Dec. 26) 1953.

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Bargen, J. A.: Med. Clin. North America, 33:935 (July) 1949.

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Personal communication (Apr. 12)

1951 After-control data 1949 from 119 patients treated with Azulfidine prior to 1944 showed 90 patients (84%) symptom-free or considerably improved.

Svartz, N.: Acta Med. Scandinav. 141:172, 1951.

1952 In a series of 52 patients with chronic ulcerative colitis 30 or 58% showed significant improvement after treatment with Azulfidine.

Morrison, L. M.: Gastroenterology 21:133, 1952.

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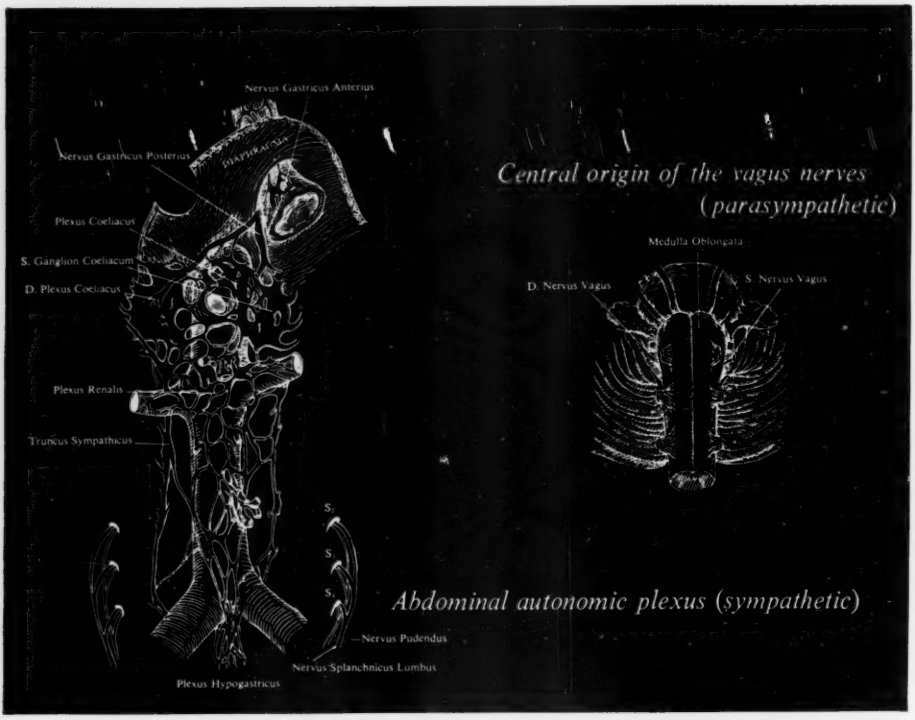

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VOLUME 94 SEPTEMBER 1954 NUMBER 3

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Editorials

HEPATIC COMA

Its Current Status

FOR MANY centuries it has been observed that patients with disease of the liver at times lapse into a deep sleep and die. It also has been recognized for a long time that some of these patients exhibit peculiar nervous and mental reactions prior to going into the state of unconsciousness known as "hepatic coma." For these reasons some relationship between the liver and the brain was postulated early. For many years little attention was paid to this type of coma, chiefly because it was nearly always fatal and to most observers simply represented the terminal phase of a hopeless disease.

Chester Jones [1] in 1936 first emphasized the value of glucose in the treatment of liver failure. Although spontaneous recovery from hepatic coma had been reported prior to this time, since 1936 it has been observed not infrequently, and interest in this subject has mounted. A few years later [2] some biochemical studies on hepatic coma were reported and it was postulated that this syndrome might be the result of a breakdown in the normal process of carbohydrate metabolism. Since that time several papers have tended to clarify this interesting syndrome.

Some authors have reported that the electrolyte levels of the blood are usually normal, while others have observed a frequent fall in the levels of serum potassium and magnesium. At times other cations are altered. Apparently mild metabolic acidosis is present, and a high organic acid fraction in the blood is encountered rather frequently, both in impending and deep coma. Pyruvic acid is often increased in both the peripheral blood and spinal fluid. The concentration of ketoglutaric acid is also often increased, as is the level of ammonia in the blood.

In 1949 the neuropathologic changes incident to severe liver disease were first reported. The most important neuropathologic change noted was a diffuse hyperplasia of protoplasmic astrocytes in the cerebral cortex, lenticular nuclei, and so forth, with little or no visible alteration in parenchymal structures. The peculiar clinical neurologic changes for so long poorly described have now been classically documented by Adams and Foley.* The electroencephalographic pattern of this type of patient in coma is somewhat characteristic [3] and at times may be of aid in the differential diagnosis of coma. The first change noted in this peculiar pattern appears to be a slowing and disorganization of alpha rhythm.† In this deep sleep, called "coma," the cerebrospinal fluid pressure is normal, as are the blood pressure, pulse rate, and, usually, respiration. Frequently, however, the amount of protein in the spinal fluid is increased, and at times so is the level of bilirubin.[4]

* Cited in Reference 3.

† Bickford, R. G., and Butt, H. R.: Hepatic Coma: The Electroencephalographic Pattern, unpublished data.

As early as 1849, Rokitansky [5] first described tyrosine and leucine crystals on the cut surface of the liver in fatal cases of acute yellow atrophy, and Frerichs [6] in 1860 isolated these amino acids in crystal form from the urine of patients dying in hepatic coma. Although such information has been common knowledge for nearly a century, little productive work was accomplished in this field until partition paper chromatography was developed. This method has enabled study of many amino acids occurring in body fluids.

In cases of hepatic coma chromatographic studies have demonstrated marked increase in the amino acids in the plasma and urine. In the plasma cystine, methionine, and glutamic acid are usually increased. In the urine cystine is almost invariably elevated and β-amino-isobutyric acid frequently is.[7] The glutamate in the cerebrospinal fluid of such patients [8] is rather markedly increased, and similar findings have been noted in dogs following hepatectomy.

In a majority of cases with hepatic coma there is an increase in the concentration of free amino acids which usually is concomitant with the severity of the coma. However, to date no consistent changes have been observed in the amino-acid pattern.‡

It is said that glutamic acid is the only amino acid metabolized by brain tissue and that it is deaminated to α-ketoglutaric acid. Walshe,[8] in 1951, using chromatographic technic, demonstrated an increase in the content of glutamine in the cerebrospinal fluid of three patients in hepatic coma. More recently, Flock and her associates [9] have noted that the amount of free glutamine in the brains of dogs after hepatectomy increases to approximately five times normal value within 24 hours. However, the signs and symptoms commonly associated with hepatic coma did not occur in these animals.

It has been long known that the feeding of diets high in protein shortens the survival time of animals with severe liver injury.[10] It has been further known that some patients with cirrhosis of the liver may have elevated levels of ammonia in the blood and that some patients with cirrhosis have an intolerance of certain nitrogenous substances. A syndrome indistinguishable from hepatic coma has been reported in patients with cirrhosis given certain ammonium-containing cation exchange resins,[11] ammonium chloride, urea, or a diet high in certain proteins.[12] The cause of the reaction was not apparent, but it was suggested that the effects might be due to ammonium intoxication. Mann and his associates have reported data which indicate that depressed hepatic function does not seem to be responsible for the increase of ammonia in the blood. Rather, the elevation of ammonia is most likely the result of the bypassing of the liver by the portal circulation and the decreased hepatic blood flow.§

Glutamic acid in the brain is thought to be important in the removal of intracellular ammonia and in altering permeability of the cell membranes to potassium ions. From these more recent biochemical studies this glutamic acid-glutamine metabolic cycle emerges as a hypothesis to explain hepatic coma, but it certainly has not been proved as yet.

---

‡ Wu, C.; Bollman, J. L., and Butt, H. R.: Changes in Free Amino Acids in Hepatic Coma, unpublished data.

§ Mann, J. D.; Bollman, J. L.; Huizenga, K. A.; Farrar, T., and Grindlay, J. H.: Blood Ammonia: Experimental and Clinical Study in Abnormalities of the Liver and Portal Circulation, unpublished data.

It seems probable that increases in blood pyruvic acid, α-ketoglutaric acid, glutamine, and ammonia in hepatic coma are reflections of some more fundamental disturbances in enzyme systems. That these changes are responsible for the cerebral dysfunction of hepatic coma has not been proved.

Hepatic coma remains a most serious and frequently fatal condition. There is no specific treatment, in spite of our increase in knowledge of the syndrome. Anticipation of and early recognition of the condition are most important in its management. Some physicians have reported spectacular responses from cortisone, human serum albumin, chlortetracycline, sodium glutamate, and various combinations of therapeutic agents. Others || have reported equally spectacular failures on use of the same agents. One seriously doubts that such advances as are described will make for spectacular treatment of a condition that often represents serious and frequently irreversible hepatic injury. But such advances in knowledge certainly lead to better understanding of the physiologic principles underlying failure of a specific organ.

HUGH R. BUTT, M.D.

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RADIOACTIVE ISOTOPES IN MANAGEMENT OF CARCINOMATOSIS OF SEROUS BODY CAVITIES

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THE CONTINUING, accelerating struggle for mastery over malignant diseases in the human has resulted in some tendency to overlook the need for and the availability of weapons with which we may attempt to achieve palliation. By and large this field of endeavor has been all too eagerly reserved for those few persons who have grasped the responsibility which actually rests upon all of us. Admittedly, such a solution has much genuine merit, however, available personnel and facilities are so meager for the problem at hand that many victims of cancer receive little or no considerate, planned therapy aimed at the production of a maximum degree of aid and comfort.

The onset of intractable effusion in one or more of the serous cavities is a distressing complication of advancing malignant disease. The true frequency with which such a state is reached cannot be estimated with accuracy; however, Clark [1] has reported that significant degrees of effusion have been observed in 29% of 266 consecutive autopsies of men who had malignant disease. In the past our efforts to provide symptomatic relief for these suffering patients have met rather indifferent success.

The intracavitary use of radioactive isotopes for the control of malignant effusions was employed by Müller, in 1945, and he reported his observations in 1949.[2] At the latter date an increasing interest in the possibilities of such a form of treatment was manifested in other circles, and there have been several reports of the results achieved and of investigations of the physical phenomena involved. Our own initial experiences have been reported previously,[3] and a subsequent analysis of further observations was presented at a later date.[4] At the outset, radioactive iodine was employed in our work. However, radioactive colloidal gold has been used exclusively

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since late in the year 1950, and the results which are reported in this communication have been compiled exclusively from the records of patients who have been treated with the latter isotope.

The indications for treatment have been simple, namely, the presence of an intractable pleural or peritoneal effusion due to proved malignant disease. Conclusive evidence of the presence of cancer has not been easy to obtain in many instances, and we have been compelled to refrain from succumbing to the temptation to attempt palliation when the suspicion has been great but microscopic data have been lacking. The fluid has been examined in each instance, and the presence of malignant cells has been the accepted criterion for treatment. In the absence of demonstrable cells in the fluid, biopsy proof from the primary lesion or from a

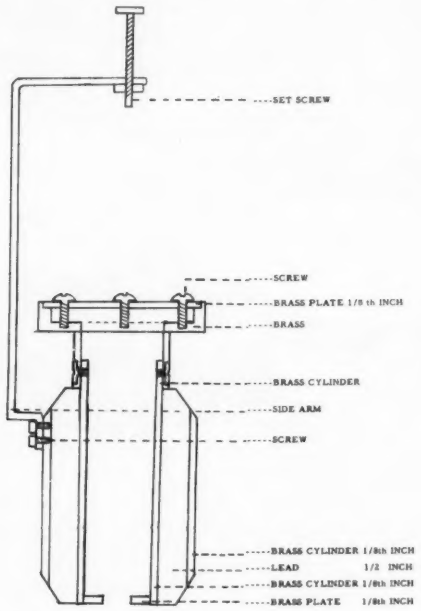

Fig. 1.—Diagram of construction of tubular protecting shield which covers the injection syringe of 50 cc. capacity.

metastasis has been required. In the case of pulmonary cancer, positive cytological evidence from sputum or by bronchoscopic aspiration has been accepted.

The technique of administration has undergone changes in our hands only in respect to the details of construction of devices employed for the protection of those who handle the radioactive isotope. At present we are using two types of protective shields which cover the injection syringe. The simplest of the two consists of a complete jacket made of lead $\frac{5}{16}$ in. (7.95 mm.) thick, which covers the barrel of a 30 cc. syringe. Studies of the effectiveness of this shield reveal that 7.5 milliroentgens of gamma radiation per minute pass through the lead jacket. Since the syringe is handled for less than one minute by the operator, the exposure to the operator's hands is below a hazardous level.

The second type of protective covering is constructed of a ½ in. (12.7 mm.) thick lead tube * which is lined on the inside and covered on the outside with ⅛ in. (3.18 mm.) thick brass (Fig. 1). The protection afforded by this jacket is approximately double that of the simpler design, and any standard 50 cc. syringe may be used within it.

The injection into the pleural space has usually been carried out after withdrawal of a major part of the fluid by ordinary thoracentesis techniques. A "Y" connector is then attached to the needle, and either the radiogold or a solution of sterile isotonic sodium chloride solution may be passed into the pleural space (Fig. 2). When radiogold is injected into the peritoneal cavity, paracentesis is carried out as usual,

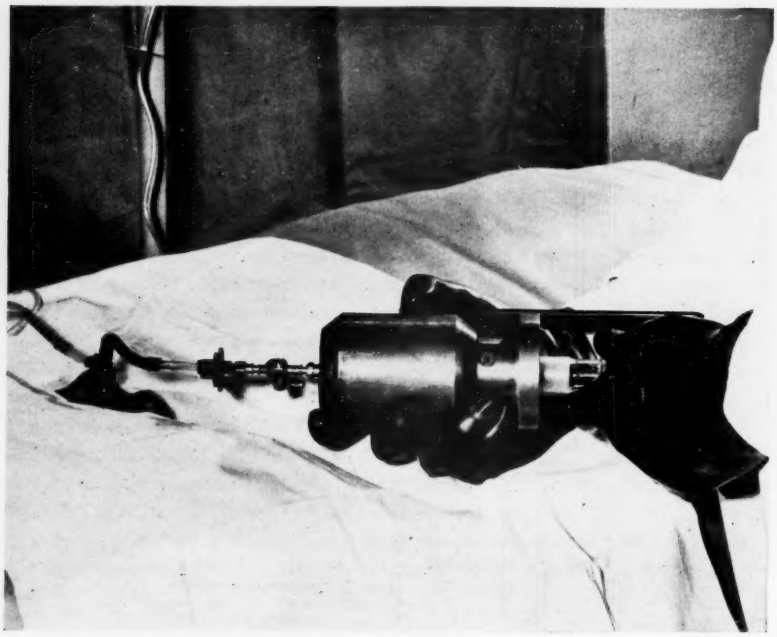

Fig. 2.—The injection of radiogold into the pleural space. A "Y" connector is attached to the thoracentesis needle, into which may be passed either the isotope or sterile isotonic sodium chloride solution. The injection syringe is covered with a protecting shield.

by means of a small trocar and cannula, and after the withdrawal of ascitic fluid a small polyethelene tube is passed through the cannula, which is then withdrawn over the tubing. The isotope injection is made through the tubing, and, upon completion of the act, the latter is withdrawn and the trocar wound is closed with one or two fairly deeply placed sutures.

The dose employed is arrived at by empirical means. Gradually, we have adopted a standard figure of 100 mc. for both the pleural space and the peritoneal cavity. This happens to conform with the practice reported by Seaman and his associates.[5] In some instances (44%) we have given more than a single dose of Au^{198}. The decision has been based upon failure of the first treatment in a patient who otherwise

* Designed by Dr. Paul R. Ritter.

appears to be holding his own in his struggle with cancer. The second injection has usually been given within three weeks after the first; however, there has been one instance of secondary treatment for recurrence of effusion nine months after an initially successful primary dose.

At times, there is necessarily some modification of the dose, depending upon the total available quantity of radioactive colloidal gold and the number of patients among whom it must be distributed. The isotope solution containing 100 mc. is diluted to 20 cc. with sterile isotonic sodium chloride solution and is delivered in lead containers, the walls of which are 1⅛ in. (28.62 mm.) thick.

The fate of radiogold after injection into a serous body cavity has been investigated by Andrews, Root, and Kniseley.[6] These workers obtained evidence that the radiogold becomes fixed in a superficial position on the pleural surfaces, possibly by means of a property of the colloid in relation to the surface, aided and abetted by phagocytosis of gold particles by macrophages on the walls of the pleural space or peritoneal cavity. Additional studies have been reported by Kniseley and Andrews,[7] which lend further support to the above observations.

Chamberlain[8] has calculated that the beta dosage at the surface is roughly 900 equivalent roentgens for each 1 mc. spread over 1,000 sq. cm. This means that if 100 mc. were injected intraperitoneally in an average adult, with a peritoneal surface area of approximately 30,000 sq. cm., the surface dose would average 3,000 equivalent roentgens if all of the radiogold were deposited on the surface. Accordingly, in the pleural space an equivalent dose of isotope should provide a considerably greater surface dose. Actually, the many variables and unknowns at work render fruitless present efforts to provide accurate calculations of radiation dosage in this method of therapy.

While it has been assumed that the mode of action of colloidal gold in suppressing malignant effusions is the result of superficial radiation damage, conclusive evidence is still lacking. Indeed, it is quite possible that the explanation will escape us until more is known about the mechanism of formation of fluid under these circumstances. Evidence is at hand, however, which indicates that the beta emanation is the effective property and that the gamma emissions are probably of comparatively minor importance in this regard. It is known that the half-life of radioactive colloidal gold is 2.7 days and that the maximum penetration of the beta particle is 3.8 mm. in tissue. The latter properties suggest that the effectiveness is a surface mechanism, and indeed it is believed that the effective tissue penetration does not exceed 1 mm.

The criteria employed for the evaluation of results have been simple. An excellent outcome has been designated only in those patients who have had no further need for the aspiration of pleural or peritoneal effusion. In those instances which have required one or two taps after therapy, the result has been designated as improved. When fluid formation continued, even though somewhat less rapidly, the case has been recorded as a failure of treatment. The final classification includes those patients who lived less than a month after treatment, thus making evaluation difficult.

This report is based upon observations made in a total number of 163 patients who received intracavitary radiogold for the control of malignant effusions in the serous cavities. Of these, 112 patients were victims of an intractable pleural effusion, and analysis of the proved primary sites (Table 1) reveals that in the majority these were either in the lung or in a breast. Thirty-nine of the patients whose malignant

TABLE 1.—*Summary of Analysis of Primary Site in Group of 112 Patients Treated for Carcinomatous Pleural Effusion*

Primary Site	Patients, No.	Primary Site	Patients, No.
Breast	47	Leukemia	2
Lung	47	Cervix	2
Lymphoma	4	Undetermined	2
Uterus	3	Larynx	1
Ovary	3	Stomach	1

TABLE 2.—*Evaluation of Results Achieved in Thirty-Nine Patients (Now Dead) Whose Pleural Effusion Arose from Pulmonary Neoplasms*

	Patients, No.
Excellent	16 (41%)
Improved	5 (12.8%)
Failures	10
Died in less than 1 mo.	8

TABLE 3.—*Results of Treatment in Thirty-Eight Patients (Now Dead) with Intractable Pleural Effusion Which Arose from Carcinoma of the Breast*

	Patients, No.
Excellent	20 (52.6%)
Improved	6 (15.8%)
Failures	5
Died in less than 1 mo.	7

TABLE 4.—*Analysis of Results of Treatment of Pleural Effusion in Twenty Patients Who Are Now Living*

	Patients, No.	%
Carcinoma of lung (8 living, 1 to 32 mo.)		
Excellent	6	30
Improved	2	10
Failures	3	15
Carcinoma of breast (9 living, 1 to 36 mo.)		
Excellent	5	25
Improved	2	10
Failures	2	10

TABLE 5.—*Primary Site of Malignant Disease in Fifty-One Patients Who Have Received Radiogold for Control of Carcinomatous Ascites*

	Patients, No.		Patients, No.
Ovary	33	Breast	1
Stomach	3	Lymphosarcoma	1
Sigmoid	3	Neuroblastoma	1
Pancreas	3	Hepatoma	1
Fundus	2	Chorioepithelioma	1
Cervix	2		

pleural effusions were secondary to pulmonary cancer have died, and the results of treatment can be evaluated (Table 2). Forty-one percent were found to have excellent results, and 12.8% were improved.

Comparable degrees of palliation have been achieved in a group of 38 patients who are now dead and in whom the primary site was carcinoma of the breast (Table 3). Fifty-two percent of this group have been classified as receiving an excellent result, and 15.8% were improved.

The survivors among the patients treated with radiogold for pleural effusion due to carcinomatous metastases or extension total 20 patients (Table 4). The duration of life after therapy has extended as long as 3 years in one instance and 32 months in another. Seventy-five percent of this group of survivors have received either an excellent or an improved result.

Of the 51 patients who were treated for carcinomatous ascites, the primary site was found to be the ovary in 65%. The remainder of the primary lesions arose in a variety of areas and include several types of malignant neoplasms (Table 5). The results of treatment have been found to be approximately comparable to those which have followed the use of radioactive colloidal gold in carcinomatous pleural effusions

TABLE 6.—*Results in Thirty-Six Patients with Carcinomatous Ascites (Now Dead)*

	Patients, No.
Excellent	17 (44.7%)
Improved	6 (16.6%)
Failure	6
Died in less than 1 mo	7

(Table 6). In all, 60% were classified as having benefited from an excellent result or were considered to have been improved. There are 15 patients living who have been treated with intraperitoneal radiogold, and 73% have been classified as excellent or improved.

Strange things happen during the life cycle of cancer in some instances, and some unusual observations have been made in a few patients from this total group of 163. One young woman was treated three years ago for carcinomatous effusion in the right pleural space and for a simultaneous ascites. The primary lesion had been in the left breast, which had been removed two years previously. She is still alive, although three areas of subcutaneous metastases have been excised during the survival period. A 59-year-old man was seen with a grossly bloody intractable right pleural effusion. No malignant cells were demonstrated by examination of numerous specimens of the effusion. A right thoracotomy was performed more than 18 months ago, and hundreds of nodular tumors were found on the surface of both the parietal and visceral pleura. These masses varied from a size barely visible to the eye to 1.5 cm. in diameter. Microscopic study revealed the presence of papillary adenocarcioma, but the primary site has not been identified. During his convalescence following exploratory thoracotomy, 150 mc. of Au^{198} was injected into the right pleural space. The patient is alive and clinically well today, and none of the many tumor implants are visible on the chest roentgenogram. Not one aspiration has been done since treatment, and there has been no fluid in the pleural space.

Toxic manifestations have included mild rather brief episodes of what appears to be radiation sickness. There have also been instances of mild hemopoietic suppres-

sion, as shown in the leucocyte count. Andrews and his associates [6] have emphasized that it is difficult to be certain of the cause of anemia in such patients. Therefore, lowered red blood cell counts have not been accepted as reliable evidence of toxicity.

Subcutaneous leakage of Au^{198} after injection resulted in cellulitis in one patient. Leakage of radiogold to the cutaneous surface occurred in two instances, and a typical radiation erythema was followed by characteristic pigmentation of the exposed skin area.

SUMMARY

We have presented our experiences with the use of radioactive colloidal gold in the management of carcinomatous effusions in the serous cavities. Favorable results have been observed in approximately one-half of a total group comprising 163 followed patients. The technique has been described, and it is comparatively simple to carry out. Toxic manifestations have been quite mild and rather rare. The methods employed for the protection of involved personnel are shown.

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SUBJECTIVE MANIFESTATIONS OF ACUTE CORONARY OCCLUSION OR INSUFFICIENCY

Their Relation to Area of Resulting Myocardial Injury

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EVER SINCE 1768, when Heberden [1] introduced the term "angina pectoris" to describe "a disorder of the heart marked with strong and peculiar symptoms and a sense of strangling and anxiety," the term has occupied a prominent place in medical literature. The underlying causes of the syndrome were a matter of speculation until the turn of the century. Satterthwaite,[2] in his textbook "Diseases of the Heart and Aorta," published as late as 1905, quotes various authorities of the 19th century who attributed the condition to disease of the pneumogastric, to infiltration of the cardiac plexus, to functional neurosis, to nerve explosion like that of epilepsy, to phrenic and intercostal irritation, to bronchiothoracic neuralgia, and to aortic disease. Although he also quotes many authors who considered the condition to be due to coronary disease, he commented on the relative rarity of angina pectoris compared with the great frequency of coronary disease found at autopsy. Leyden and especially Huchard, in the 1880's, however, definitely recognized the causal relationship of coronary disease and angina pectoris. Huchard spoke of narrowing and obliteration of the coronary arteries resulting in ischemia of the heart as the underlying cause.

Although the strangling, vise-like pain and other chest symptoms were the features that attracted the attention of all later observers, some authors noted additional symptoms as being part of the picture. Osler [3] mentions profuse sweat, gray pallor, exhaustion, the rare occurrence of syncope, and dyspnea with wheezing. Mackenzie [4] observed sweating of the body, flushing, vomiting, salivation, gaseous eructation, and increased flow of urine.

It was not until Herrick * described the clinical manifestations of acute coronary occlusion, which stimulated subsequent intensive studies by numerous workers, that the anginal syndrome was definitely correlated with acute manifestations of coronary disease and that the symptoms as originally described by Heberden and other later writers were found to be far from all-inclusive. Many cases present symptoms which have no resemblance to the anginal syndrome as originally described.

I have observed some patients who had two or more attacks of acute myocardial infarction located in different regions of the left ventricle, each attack having different subjective manifestations. The following is an example:

A 65-year-old man, who had had asymptomatic hypertension for several years, developed a sensation of faintness and impending death, with cold clammy perspiration, lasting a few minutes and followed by a sensation of very mild pressure in the retrosternal region lasting

* References 5 and 6.

several hours. An electrocardiogram revealed acute posterior left ventricular wall infarction. He made good recovery and except for occasional slight retrosternal pressure on fast walking or with excitement felt comfortable. About five years after the first attack, he developed a severe attack of constricting pain in the right upper arm, radiating across the anterior chest and into the interscapular region, lasting 15 minutes. The pain recurred in the same locations several times during the following two days, each attack lasting 5 to 10 minutes. An electrocardiogram obtained at this time revealed acute anteroseptal left ventricular wall infarction extending to the lateral wall of the left ventricle.

Observations such as these prompted me to study the records of a series of cases, to determine if the location of myocardial injury had any bearing on the presenting symptoms in different cases. This paper covers such study.

MATERIAL AND DIAGNOSTIC CRITERIA USED

The series consisted of 1,200 cases selected from my files. The histories in these cases were carefully obtained by myself. Each case ran the characteristic clinical course and showed electrocardiographic evidence either of acute coronary occlusion with myocardial infarction or of acute coronary insufficiency with or without myocardial necrosis. Some of the cases came to autopsy, which confirmed the diagnosis.

The location of infarction was determined by the following currently accepted electrocardiographic patterns: Anterior left ventricular wall infarction was determined by the appearance of a Q wave and the evolution of a negative T wave, with coving and elevation of the QRS-T segment in Lead I or Leads I and II and corresponding depression in Lead III; there is a QS wave with elevation and coving of the QS-T segment and evolution of a negative T wave in Leads V_1 through V_3 or V_4 in anteroseptal involvement; there is elevation and coving of the QS-T segment with evolution of a negative T wave in Leads V_4 through V_6 in anterolateral involvement, and there are QS-T segment changes with evolution of a negative T wave in all precordial leads in anteroseptal involvement extending to the lateral wall. Posterobasal left ventricular wall infarction was shown by the appearance of a Q wave and the evolution of a negative T wave with coving and elevation of the QRS-T segment in Lead III or Lead II and III and corresponding depression in Lead I as well as high-voltage T wave in Leads V_2 through V_4. If the QRS-T-segment changes and the evolution of the negative T wave occurred also in Lead V_6 or V_4 to V_6 lateral involvement was considered in addition.

Acute coronary insufficiency was indicated by negative or diphasic T-wave changes, associated in most cases with depression of the QRS-T segment in the conventional, unipolar extremity aV_L and aV_F leads and in the precordial leads and often also by a positive T wave in lead aV_R. The alterations were usually of comparatively short duration and shifted in the various leads from time to time. In many cases the QRS-T-segment depression was very marked, and in none were there any reciprocal changes in Leads I and III. The presence or absence of necrotizing changes was determined from the clinical course. If there was no elevation in temperature and if the sedimentation rate and white blood cell count were normal in the presence of the electrocardiographic changes, ischemia without necrosis was considered to be present. Any elevation in temperature, increase in the white blood cell count, or acceleration of the sedimentation rate was considered evidence of necrotizing myocardial changes, after other disease that might account for these findings was ruled out.

OBSERVATIONS

The 1,200 cases in this series consisted of 974 of myocardial infarction and 226 of myocardial ischemia or ischemic necrosis. The location of infarction in the 974 cases was anteroseptal in 67, anteroseptal and lateral in 341, anterolateral in 117, posterobasal in 395, and posterolateral in 21. In 33 cases there was infarction in both the anterior and posterior walls at the same time.

Inasmuch as the number of cases in the groups with anteroseptal, anterolateral, and posterolateral involvement was small, it was deemed advisable to classify all

cases into the following four groups: those with anterior wall infarction, including anteroseptal, anterolateral, and both anteroseptal and anterolateral involvement; those with posterior wall infarction including posterobasal and posterolateral involvement; those with combined anterior and posterior wall involvement, and the group with coronary insufficiency.

The most interesting observation was the great variation in complaints in the different cases. Although the main pattern was similar in most cases, the details of complaints varied markedly from case to case. Some experienced severe pain in the precordium; others, in the entire anterior chest; still others, in the upper sternal, midsternal, or lower sternal regions or in the entire length of the sternum. In some it was localized in the back of the chest, neck, arms, and so on. Radiation likewise varied from person to person. Various combinations of other symptoms, singly or in groups, accompanied the pain or occurred independently, such as sweating, dizziness, faintness, unconsciousness, restlessness, weakness, choking, dyspnea, palpitation, gaseous eructation and so on.

We shall attempt to describe the individual complaints, their incidence, and their possible relation to the location of myocardial damage.

Pain.—This was the commonest complaint. In the entire series of 1,200 cases, 1,147, or 95.6%, had this complaint. Although some patients had difficulty describing the character of pain they suffered, most gave clear descriptions. The various terms used were heaviness, tearing, cutting, tingling, burning, pinching, constricting, pressing, cramping, depressed, oppressive, tightening, squeezing, stiffening, vise-like, crushing, strangling, and dragging. Some complained of a sensation as if "the chest is locked" and a feeling as being crushed to death or "something was ripping apart," associated with loss of breath. In 35, or 2.9% of cases, pain was very mild or insignificant, being described rather as a feeling of numbness, raw sensation, or dull ache. In the vast majority of cases the pain was localized in the anterior chest. In 99, or 8.3%, pain was in areas outside the anterior chest, as in one or both arms, shoulders, interscapular area, left scapular area, neck, head, jaws, gums, teeth, wrists, throat, epigastrium, abdomen, and other remote regions. In 53, or 4.4%, there were no complaints of pain or anything resembling pain in any region of the chest or body. If we add the 53 cases with absolutely no pain, the 99 cases in which pain was located in other areas than the anterior chest and could therefore be missed in the history, and the 35 cases in which there were mild sensations other than actual pain, the total number of cases in which pain was of no help in the diagnosis was 187, or 15.6% of the entire series of 1,200 cases. In many other cases the pain was not of the characteristic constricting type and was not of definite help in the differential diagnosis.

A comparison of these figures with the incidence of so-called atypical or painless angina reported in the literature reveals considerable difference in some of the reports. Pollard and Harvill,[7] in a series of 375 cases, found that 4.5% had no pain. In Warren's [8] 200 cases, 16 cases, or 8%, had either the so-called atypical angina or gave no history of pain. In Papp's [9] 150 cases about 10% had no pain or very slight pain. In 255 autopsy cases reported by Landman and co-workers [10] 11% had no pain. All these correspond to our figures. On the other hand, in 274 cases reported by Rothe[11] 31% had no history of pain, and in 100 cases reported by Chambers [12] 30% had no history of pain. Forbes,[13] in a series of 167 autopsy cases, reports

35% without a history of pain and 12% more with a history of vague pain of doubtful origin. In 100 autopsy cases reported by Gorham and Martin [14] as many as 42% had no pain record. The high figures in the last four reports are probably due mainly to the fact that the hospital histories from which the authors obtained their data were not recorded in sufficient detail, especially as to preexisting pain, if mild. This is the opinion also of Wolferth,[15] who observed in his practice very few cases without pain. It speaks for the unreliability of some hospital histories.

To determine whether there is any relationship between the location of pain and the area of myocardial damage, our cases were classified into those in which pain was felt in the entire anterior chest, those in which it was felt in the precordial region only, those in which it was felt in the retrosternal region only, those in which it was felt in areas outside of the chest and those in which there was no pain at all; these locations of pain were then related to the location of the myocardial damage. Table 1 shows these relationships. Although the differences in the figures are not very striking, it appears that pain felt in the entire anterior chest and in the retrosternal region occurs more frequently in anterior than posterior wall infarctions, while the

TABLE 1.—*Location of Pain in Relation to Area of Myocardial Injury*

Areas of Myocardial Injury	All Cases		Cases with Pain		Location of Pain								Cases Without Pain	
					Anterior Chest		Precordial		Retrosternal		Other Regions			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Left ventricle	1,200	100	1,147	95.6	288	24.0	374	31.2	386	32.2	99	8.3	53	4.4
Anterior wall	525	43.8	511	97.3	149	28.3	150	28.5	169	32.2	43	8.2	14	2.5
Posterior wall	416	34.6	395	95.0	85	20.4	138	33.2	126	30.3	46	9.6	27	6.5
Anterior and posterior walls	33	2.8	32	97.0	5	15.2	11	33.3	16	48.5	0	0.0	1	3.0
Coronary insufficiency	226	18.8	215	95.1	49	21.7	75	33.2	75	33.2	16	7.1	11	4.8

painless form and those instances of pain localized to the precordial region and in areas outside of the anterior chest are more frequent in posterior than anterior wall infarction. In combined anterior and posterior wall infarction precordial as well as retrosternal pain occurred somewhat more frequently. The number of cases here was too small, however, from which to draw conclusions. The location of pain in coronary insufficiency follows about the same pattern as in infarction.

Pain radiated from its point of origin most frequently to the various parts of the upper extremities and to the back of the chest. The radiation occurred either to one or both arms; one or both forearms; one or both wrists; one or both shoulders, elbows, palms, or fingers, and to the left scapular or interscapular regions. In two cases it radiated to both the upper and lower extremities, and in one, to the kidney region. Radiation of pain to the head, as the temples, face, ears, frontal region, nose, jaws, gums, teeth, and throat, and to the neck was relatively infrequent. Radiation to the epigastrium or abdomen was more frequent. Radiation to more than one area often occurred. In many cases, the sensation felt in the area of radiation was different than in the area of its origin. In some cases the main pain originated outside the chest and radiated to the anterior chest region.

The relationship between the areas to which pain radiated and the location of myocardial injury is shown in Table 2. It will be seen that there are no marked differences in the areas of radiation in anterior and posterior wall infarction, although

there is a greater tendency for pain to radiate to the neck, upper extremities, and epigastrium in posterior wall infarction. Radiation of pain in coronary insufficiency occurs more frequently than in gross myocardial infarction, and this is to the upper extremities and back more frequently than to other regions.

Organic Disturbances.—Subjective complaints referable to general constitutional and local organic disturbances were very frequent in our series.

Among the general constitutional disturbances, sweating occurred in as many as 62.9%; weakness or tiredness, in 18.2%, and other disturbances, such as chills, heat sensation, flushing, and shivering, in 7.2% of all cases. A desire to urinate occurred in four cases.

TABLE 2.—*Radiation of Pain in Relation to Areas of Myocardial Injury*

					Radiation of Pain									
	All Cases		Cases with Radiation		Head		Neck		Upper Extremities		Back		Epigastrium	
Areas of Myocardial Injury	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Left ventricle	1,200	100	760	63.3	32	2.6	46	3.8	385	32.1	219	18.2	78	6.5
Anterior wall	525	43.8	330	62.9	16	3.1	16	3.1	161	30.7	98	18.7	39	7.4
Posterior wall	416	34.6	258	62.1	10	2.4	20	4.8	133	32.0	71	17.1	24	9.3
Anterior and posterior walls	33	2.8	16	48.5	2	6.1	2	6.1	7	21.2	5	15.1	0	0.0
Coronary insufficiency	226	18.8	156	69.1	4	1.8	8	3.6	84	37.2	45	19.9	15	6.6

TABLE 3.—*Frequency of Organic Disturbances in Relation to Areas of Myocardial Injury*

			Organic Disturbances											
	All Cases		Sweating		Weakness		Other Constitutional Disturbances		Cerebral		Gastrointestinal		Respiratory		Cardiac	
Areas of Myocardial Injury	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Left ventricle	1,200	100	755	62.9	219	18.2	76	6.3	259	21.6	189	15.8	136	11.3	25	2.4
Anterior wall	525	43.8	344	65.5	97	18.5	27	5.2	106	20.2	88	16.7	56	10.6	10	1.9
Posterior wall	416	34.6	273	65.6	83	19.8	24	5.8	120	28.6	77	18.5	48	11.5	8	1.9
Anterior and posterior walls	33	2.8	15	45.4	3	9.1	8	24.2	4	12.1	1	3.3	5	15.1	1	3.3
Coronary insufficiency	226	18.8	123	54.4	36	15.9	17	7.5	29	12.8	23	10.2	27	11.9	6	2.6

Symptoms of cerebral origin occurred in as many as 21.6% of cases. They consisted of dizziness, light headedness, restlessness, apprehension, faintness, stuporous state, syncope, and complete unconsciousness, with occasional instances of local tonic or clonic convulsive movements. Some of the cerebral manifestations, particularly syncope, have been reported by other authors. Huber † was apparently the first to observe the association of syncope with the anginal syndrome, as long ago as 1888. Galavardin [17] cited six cases of the Adams-Stokes syndrome associated with angina pectoris in 1922. More recently, Cookson [18] observed 15 cases of syncope among 200 cases of myocardial infarction. Bean and Read [19] report eight cases of myocardial infarction in which cerebral symptoms obscured all other manifestations of the disease.

† Huber, W., cited by Dock.[16]

Symptoms referable to the gastrointestinal tract occurred in 15.8% of cases. They consisted of nausea, vomiting, gaseous eructation, "heartburn," epigastric heaviness, "indigestion," and complaints such as "sick stomach," "full of gas," or bloating, and occasionally a desire for bowel movement was a complaint. There were infrequent complaints of salivation and of dryness of the mouth.

Respiratory symptoms were present in 11.3% of cases. They included dyspnea, choking, difficulty in catching breath, cough, and dryness in the throat. Some persons described a feeling of being unable to catch the breath.

Subjective complaints referable to the heart, besides the pain, occurred in only 2.4% of cases. They included palpitation and a sensation of "pounding" or "thumping."

The incidence of the various organic disturbances in relation to the area of myocardial injury is shown in Table 3. It will be observed that sweating, weakness, and cerebral and gastrointestinal disturbances occur less often in myocardial ischemia than in gross myocardial infarction. Sweating occurs with equal frequency in posterior and anterior left ventricular wall infarction. Weakness and gastrointestinal, respiratory, and, especially, cerebral disturbances occur more frequently in posterior than in anterior wall infarction.

COMMENT

Although strangling, constricting chest pain is the outstanding and characteristic complaint in an acute coronary insult, there are many other complaints occurring singly or in groups, with and occasionally without pain, which make up the subjective symptomatology of the disease. Also, the pain may vary so greatly in character, intensity, location, and radiation as to lose its anginal nature. It is therefore not surprising that the older writers considered so-called "true angina pectoris" a condition rare in comparison with the frequency of coronary disease found at autopsy.

The typical strangling, constricting, or other similarly described pain that frequently occurs in this condition appears to be a combination of pain felt on the surface of the body and that of spastic contraction of the thoracic muscles and of the smooth muscles of the thoracic and abdominal viscera. The contractions of the thoracic muscles are of reflex spinal origin and are similar to abdominal muscle spasm in acute intra-abdominal pathology. Indeed, some upper abdominal muscle spasm is occasionally observed in an acute coronary insult. Because of the bony enclosure of the thorax, the thoracic muscle contractions have the constricting effects which the abdominal muscle contractions do not have. Bronchial, esophageal, pyloric, and other sphincteric and smooth muscle spasms are of widespread vagal origin and have strangling and pressure effects.

From a physiologic viewpoint, the subjective manifestations of an acute coronary insult speak for extensive sensory receptor innervations in the heart, with emerging afferent nerve fibers making widespread communications with a system of efferent neurons. Ionescu [20] traced afferent nerve impulses coming from the heart through the inferior cardiac nerves, the stellate ganglion, the cardiothoracic nerve, the thoracic sympathetic chain, and the rami communicantes from the eighth cervical to the fifth thoracic segment. Some afferent impulses in the heart are probably carried also by the vagus, as suggested by the work of Hatcher and Weiss.[21] Many of the afferent impulses reach the local segmental areas of the spinal cord and produce the reflex muscular spasms of the thorax. The more frequent occurrence of pain in the entire

anterior chest and in the retrosternum in anterior than in posterior wall infarction and in the precordial region in posterior than in anterior wall infarction speaks for some variation in the location of the afferent neurons in the heart and in the segmental arrangement in the spinal cord. Likewise, the more frequent radiation of pain to the neck, upper extremities, and epigastrium in posterior than in anterior wall infarction is probably due to the location of the posterior basal portion of the heart in relation to the diaphragm and phrenic nerve. The close relationship of the posterior basal portion of the heart to the diaphragm may also explain the somewhat more frequent occurrence of respiratory and gastrointestinal symptoms in posterior than in anterior wall infarction. The neurons from the posterior wall probably have more frequent spinal segmental connections with those coming from the diaphragm and gastrointestinal tract.

Most of the afferent impulses coming from the heart apparently reach the hypothalamic region, where they make communications with all the vegetative nuclei, especially with the vagal system, which cause the visceral spasms, sweating, and other symptoms. Greving [22] demonstrated the presence of six major nuclear groups in the hypothalamus, which he believes are vegetative in origin. He also observed nerve communications between these nuclei and the frontal lobes, olfactory areas, and the thalamus, and he believes that the impressions they receive from the sensory receptors in various regions of the body are thus brought under higher central nervous system perception.

Libman [23] was of the opinion that the various constitutional reactions to somatic disease are dependent upon the sensitivity of the individual person. In a hypersensitive person the impulses coming from a diseased area travel more directly into the central nervous system. In a hyposensitive person they seem to be relayed in the autonomic nervous system or to linger there. He therefore considered all manifestations other than pain to be "substitution symptoms," the pain impulses being translated into autonomic nervous system disturbances, such as choking, coughing, weakness, exhaustion, syncope, sweating, and so on.

It is possible that direct local intercommunications of sections of the autonomic nervous system between the heart and other thoracic and abdominal viscera occur and may cause some of the spastic phenomena in the adjacent organs and structures induced by sensory impulses originating in the heart. However, the very spastic disturbances must be integrated in the central nervous system to be perceived by the person and expressed as symptoms. Furthermore, in our cases there were numerous instances of hyposensitive persons, as determined by the Libman test, who presented the typical anginal syndrome and of hypersensitive persons who showed other manifestations than the anginal syndrome. We must, therefore, conclude that all subjective manifestations are the products of central nervous system integration and that the variations in the symptomatic expressions of an acute cardiac insult are the results of some differences in the location and extent of sensory receptors in the heart and of synaptic connections in the central nervous system in different persons. Much depends apparently, also, upon the interpretative ability of the given person of the impulses received in the brain, which, judging from our findings, varies markedly from person to person. The occurrence of occasional cases with extensive myocardial infarction and slight subjective disturbances, as in the cases reported by Selzer [24] and other authors, and of cases of little myocardial damage with severe disturbances would tend to corroborate this theory.

Many of the subjective disturbances of an acute coronary insult, especially syncope, may be likened to the effects observed by stimulation of a hyperactive carotid sinus, as shown in a previous communication.[25] Syncope and convulsions induced by the carotid sinus reflex are due, according to Ferris and co-workers,[26] either to cardioinhibition, with stoppage of the heart, or to general vasodepression, with pooling of blood from the cerebral circulation, or to direct effect of the impulses on the brain. I [27] have observed that the cardioinhibitory effect produced by the carotid sinus reflex is due either to sinus slowing and arrest or to complete auricular-ventricular block, or to both. Syncope occurring in an acute coronary insult appears to have the same mechanisms as in the carotid sinus reflex. In a coronary insult, however, the condition may, in some cases, be due to local disturbances in the cardiac mechanism induced by interference with the blood supply to the auriculoventricular conduction apparatus or to the sinoauricular node. This would explain the greater incidence of syncope in posterior left ventricular wall involvement, where an acute insult affects either the circumflex branch of the left coronary artery or the right coronary artery, which supply blood to the auricular chambers and upper conduction system. In our series, 8.4% more cases of posterior than of anterior wall infarction showed cerebral manifestations, which may represent the percentage of cases in which the cerebral symptoms are due to local changes in the heart.

Our observations may have practical value in helping to determine the site of myocardial infarction in an acute coronary insult. Anterior left ventricular wall infarction is more likely to be present if the pain is experienced over the entire anterior chest or over the retrosternal region and its radiation is to the head or back. Posterior left ventricular wall infarction is the more likely diagnosis if pain is absent or is localized in the precordial region and/or in the presence of cerebral manifestations, especially syncope, and/or in the presence of gastrointestinal or respiratory disturbances. It must be remembered, however, that these features are based only on their relative frequency of occurrence and are not specific points in differential diagnosis of anterior and posterior wall infarction.

The early subjective manifestations of coronary insufficiency are about the same as those of coronary occlusion. In coronary insufficiency, however, they are on the average milder and more intermittent. The pain is slightly more frequent in the retrosternal region, and radiation is more frequent to the upper extremities and back and much less frequent to the epigastrium. Weakness, cerebral disturbances, and gastrointestinal disturbances are less frequent.

SUMMARY

A study of the early subjective manifestations of acute coronary occlusion and of coronary insufficiency was made in 1,200 cases. Nine hundred seventy-four of these ran a subsequent course of myocardial infarction, and 226, of myocardial ischemia or ischemic necrosis. Among the 974 cases of infarction, the location of infarction was in the anteroseptal region in 67, in the anteroseptal and lateral region in 341, in the anterolateral region in 117, in the posterobasal region in 395, in the posterolateral region in 21, and in both the anterior and posterior walls in 33.

There was a great variation of complaints in different cases. The commonest complaint was the characteristic constricting pain, which occurred in the majority of cases. In 4.4% there was no pain in any form; in 8.3% the pain was felt in other areas than in the anterior chest region, and in 2.9% the pain was very mild and

insignificant, making a total of 15.6% cases in which pain was of no help in the diagnosis. In many others the pain was not of the characteristic constricting type and was not of definite help in the differential diagnosis.

Radiation of pain was most frequent to the various parts of the upper extremities and to the back of the chest. Next most frequent areas of radiation were the epigastrium and abdomen, and least frequent, the head and neck. Frequently radiation occurred to more than one area in the same case. In two cases radiation occurred to the lower extremities, and in one, to the kidney regions. In many cases the sensation in the area of radiation was different from that in the area of its origin. In some cases the main pain originated in various areas outside of the chest and radiated to the anterior chest.

Besides pain, 62.9% of patients complained of sweating; 18.2% of weakness, and 7.2%, of other constitutional disturbances, as chills, heat sensation, flushing, and shivering. One or more cerebral symptoms, such as dizziness, light headedness, restlessness, apprehension, faintness, syncope, and occasionally local tonic or clonic convulsive movements, occurred in 21.6%. Gastrointestinal symptoms, such as nausea, vomiting, gaseous eructation, "heartburn," "indigestion," and, rarely, salivation or dryness of the mouth occurred in 15.8%. Respiratory symptoms, such as dyspnea, choking, difficulty in catching breath, cough, and occasionally dryness in the throat, occurred in 11.3%. Complaints referable to the heart, other than pain, such as palpitation, "pounding," or "thumping," occurred in 2.4%.

Pain occurred relatively more frequently in the entire anterior chest or in the retrosternal region and had a tendency to radiate relatively more often to the head and back in anterior left ventricular wall infarction than in posterior wall infarction. In the latter, pain was relatively more frequent in the precordial region and radiated relatively more often to the neck, upper extremities, or epigastrium, and it was relatively more frequently absent than in anterior wall infarction. Cerebral, gastrointestinal, and respiratory disturbances were commoner in posterior wall infarction.

Early subjective manifestations of coronary insufficiency are about the same as those of coronary occlusion, except that pain in insufficiency is on the average milder and more intermittent. It is also somewhat more frequent in the retrosternal region, and its radiation to the epigastrium is less frequent. Weakness and cerebral and gastrointestinal disturbances are less frequent.

The physiologic mechanism of the subjective manifestations is discussed. The heart is considered to have extensive sensory receptors, with emerging afferent nerve fibers making widespread synaptic connections with efferent neurons in the vegetative nuclei of the hypothalmic region. The variations in symptomatic expression of an acute cardiac insult appear to be due to differences in the location and extent of sensory receptors in the heart and of synaptic connections in the central nervous system as well as to individual differences in the interpretative ability of the higher centers.

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TETRACYCLINE THERAPY

Clinical and Laboratory Observations on One Hundred Eighty-Four Patients Treated with Tetracycline

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TETRACYCLINE is a recently developed antibiotic which has a structure [2] and antimicrobial spectrum * similar to those of chlortetracycline and oxytetracycline. To evaluate its clinical usefulness and pharmacologic properties, we have studied the effect of the oral and intravenous administration of tetracycline, as the hydrochloride, in 184 patients with acute infections.

All adults were given a dose of 2 gm. a day, and children were given 50 mg. per kilogram of body weight a day, in four divided doses at six-hour intervals. The adult patients treated orally were given an initial dose of 1 gm., and the children were given a dose of 25 mg. per kilogram of body weight, for the purpose of obtaining a higher initial serum level.

The clinical course in 153 of the 184 patients was evaluated on the basis of duration of fever, leucocytosis, subjective complaints, and objective physical findings (Table 1). The response of the remaining 31 patients could not be properly rated, because a diagnosis of bacterial infection was not substantiated.

RESULTS

Acute Bacterial Pharyngitis, Including Scarlet Fever.—Forty-two patients were treated for acute bacterial pharyngitis, including 25 patients with scarlet fever. Of the 17 remaining patients, Streptococcus pyogenes was isolated from 10; Micrococcus pyogenes var. aureus was isolated from 2; pneumococci were isolated from 2, and no pathogen was obtained from 3. The patients became afebrile in an average of 40 hours, with a range of 12 hours to 7 days. In one patient there was an associated serous meningitis with a sterile cerebrospinal fluid. The clinical course was

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* References 3-8.

consistent with the serous meningitis associated with scarlet fever described by Sweet and Lepper.[9] Scarlet fever was complicated by acute ulcerative stomatitis in two siblings. Str. pyogenes was isolated from the throat of one sibling, and a hemolytic coliform bacillus, in addition to an unidentified Gram-negative Diplococcus, was cultured from the second patient. Although nose and throat cultures were negative in both by the third day of tetracycline therapy, the oral lesions and fever persisted, as would be expected from the usual course of ulcerative stomatitis.

TABLE 1.—*Clinical Response in 153 Patients Treated with Tetracycline*

Diagnosis	Patients Treated, No.	Response		
		Satisfactory	Indeterminate *	Unsatisfactory *
Acute pharyngitis				
Streptococcic, including scarlet fever	35	33	2	..
Others	7	7	..	..
Otitis media	9	9	..	..
Acute sinusitis	1	1	..	..
Laryngotracheobronchitis	11	11	..	..
Pertussis	26	24	..	2
Pneumonia				
Pneumococcic	12	12	..	..
Others	13	13	..	..
Empyema	1	1	..	..
Meningitis, caused by				
H. influenzae	6	4	1	1
N. meningitidis	4	4	..	..
Others	6	3	2	1
Shigella dysentery	4	4	..	..
Infant diarrhea	1	1	..	..
Infectious impetigo	3	3	..	..
Pyoderma	3	2	..	1
Osteomyelitis, staphylococcic	2	..	1	1
Intraabdominal abscess	1	..	..	1
Soft-tissue infection	1	1	..	..
Acute pyelonephritis	1	1	..	..
Acute brucellosis	1	1	..	..
Pharyngeal carriers of				
D. pneumoniae	2	2	..	..
Str. pyogenes	2	2	..	..
C. diphtheriae	1	1	..	..
Total	153	140	6	7

* See text for discussion.

Otitis Media.—Tetracycline was given to three patients with acute purulent otitis media and six patients with acute catarrhal otitis media, all of whom responded satisfactorily.

Acute Sinusitis.—The single patient treated was relieved of severe frontal cephalalgia with chills and a temperature of 102 F. after 36 hours of therapy.

Laryngotracheobronchitis.—Among the 11 patients treated, the disease was predominantly a bronchitis in 5. Three patients had measles. No significant pathogens were isolated, except in two patients from whom pneumococci were cultured. The response in all 11 patients was satisfactory, and no complications developed.

Pertussis.—Twenty-four of the 26 patients responded adequately to a 10-day course of tetracycline. Although a control group of patients was not observed concomitantly, the clinical responses were satisfactory and were similar to those

observed in this hospital of patients treated with chlortetracycline under the same conditions.[10] Two patients developed significant complications. One patient continued to have fever in which the temperature spiked to 103 F. (rectal), associated with unusually severe paroxysmal cough, anorexia, and excessive irritability. Oral moniliasis developed on the seventh day of therapy. On the eighth day of oral administration of tetracycline a small area of pneumonic consolidation was found by roentgenogram. Concurrently, the patient developed acute cystitis, and a Proteus organism was isolated from the urine. After 10 days of tetracycline therapy, chloramphenicol and sulfisoxazole (Gantrisin) were substituted, because of the persistence

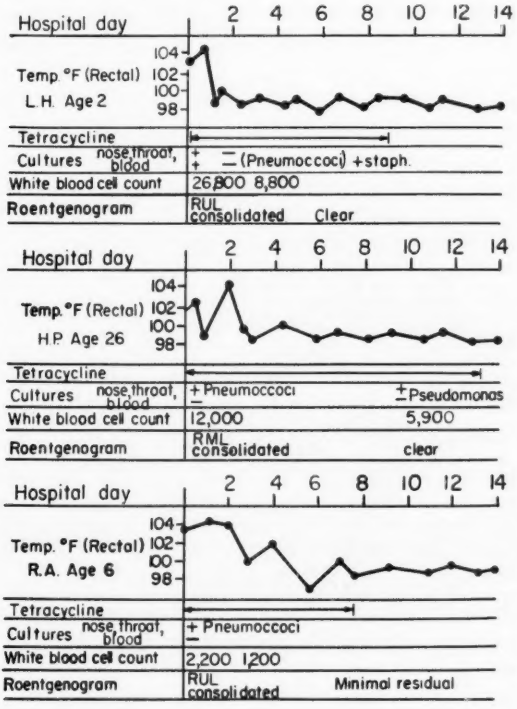

Fig. 1.—Clinical course of three patients with lobar pneumonia receiving tetracycline.

of the Proteus organism. Following initiation of the latter therapy, the pulmonary infiltrate and cystitis, as well as the protracted cough, resolved satisfactorily. The second complication occurred in a 2-year-old child with pertussis, who was treated for the first eight days after admission with tetracycline. Subsequently the patient developed rubeola, and the severity of the productive cough increased. Except for the cough, the child did not appear acutely ill. Tetracycline was again administered, because of the marked bronchitis, without obvious effect. The patient suddenly and unexpectedly died five days after the onset of the measles rash. Postmortem examination showed nothing of significance except for a severe generalized bronchitis.

Pneumonia (Fig. 1).—Twenty-two children and three adults were treated for either lobar or bronchial pneumonia. Pneumococci were isolated from the upper respiratory tract or sputum in 11 of the patients. Except for the isolation of Str. pyogenes from an additional patient, no other significant pathogens were obtained. Included in the group of 11 patients were 4 with rubeola. In none of the latter group was the titer of cold agglutinins higher than 1:64. The clinical course after the administration of tetracycline was satisfactory in all patients, and there were no complications, except in one adult, who developed marked diarrhea after five days of tetracycline administration. M. pyogenes var. aureus was isolated from the stools, and erythomycin was substituted for the tetracycline. The diarrhea stopped after four days of treatment, and the Micrococcus subsequently disappeared from the stools.

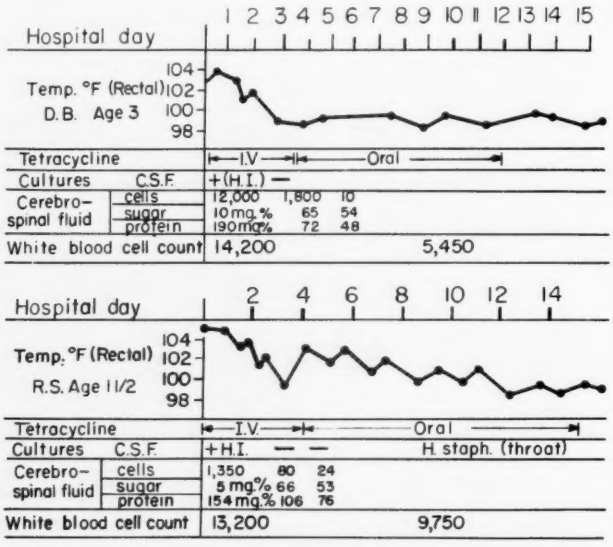

Fig. 2.—Clinical course of two patients with meningitis caused by Hemophilus influenzae receiving tetracycline.

Empyema.—One patient was treated for empyema, with a satisfactory response. An organism of a Bacteroides species was isolated from the pleural fluid; after five days of tetracycline therapy the organism could no longer be cultured. The disappearance of the Bacteroides from the pleural fluid was coincident with definite clinical improvement. As an adjunct to antibiotic therapy, the patient was given a daily instillation of streptokinase and streptodornase for one week.

Acute Purulent Meningitis (Fig. 2).—Among the 16 patients with bacterial meningitis, Hemophilus influenzae was isolated from 6. The response in four of the six, aged 6 months to 3 years, was satisfactory. One of the exceptions, a 2-year-old child, was admitted in extremis and died within 12 hours of admission, without responding. A second patient, aged 6 months, still had a spiking fever with a marked pleocytosis spinalis by the fifth day of intravenous administration of tetracycline.

The spinal fluid culture, however, was negative by the second day of therapy. Because the patient did not appear to be responding, the therapy was changed to use of chloramphenicol, and the subsequent course was satisfactory. Growth of the causative organism was inhibited by 0.8 γ of tetracycline per milliliter by the tube-dilution method.

Four patients, aged 1 to 10 years, with meningococcal meningitis responded adequately, and there were no complications. The rectal temperature remained below 100 F. after four days of treatment in three patients and after seven days in another. The delayed response of the temperature in the last patient was due, in part, to a thrombophlebitis.

In three children, aged 2, 3, and 6 years, no organisms could be cultured from the cerebrospnial fluid. The patients had each received other antibiotic therapy on the day preceding admission. The subsequent response to tetracycline was uniformly satisfactory.

A Bacteroides organism was isolated from the cerebrospinal fluid of a 17-year-old youth who had developed acute purulent meningitis and in whom a brain abscess was suspected as well in the posterior fossa following radical mastoidectomy. The patient had previously received 1,000,000 units of penicillin, 4 gm. of sulfisoxazole, and 1 gm. of streptomycin a day for two weeks without clinical response and without eradication of the Bacteroides. Subsequently, the patient was given 3 gm. of tetracycline intravenously a day for 14 days. Bacteroides could not be cultured from the cerebrospinal fluid on the 10th day of therapy or thereafter. Because of the severity of the infection and since the initial response was questionable, the dose of tetracycline was raised to 4 gm. a day, intravenously, for three additional weeks. After eight weeks of therapy, the patient dramatically improved. He became afebrile, and the cerebrospinal fluid findings were normal. To date, 10 weeks after initiation of therapy, the patient is essentially asymptomatic. The tetracycline is being continued in a dose of 3 gm. a day, by mouth, for an additional month.

There was no demonstrable effect of tetracycline in a 2-year-old patient with acute purulent meningitis associated with an infected dermoid cyst which overlay the distal spinal canal. A Proteus organism was cultured from both the cyst and the cerebrospinal fluid. The organism was still present in both sites after six days of tetracycline therapy. Subsequently, the dermoid cyst was surgically removed and the patient was treated successfully with a combination of chloramphenicol and sulfisoxazole.

The second death occurred in a 49-year-old obese alcoholic hypertensive woman, who had been ill for a week previous to admission. The patient was admitted in coma accompanied by convulsions and shock, which persisted until death although the blood pressure was maintained at normal levels with arterenol (Nor-epinephrine). The patient died on the sixth hospital day. A paracolon bacillus was isolated from the cerebrospinal fluid on admission but not from culture subsequent to the initiation of therapy. The organism was inhibited by 0.025 γ of tetracycline per milliliter. Postmortem examination revealed definite healing of the meninges. Additional pathologic findings included fatty infiltration of the liver; chronic pyelonephritis, with numerous recent disseminated renal abscesses, and bleeding esophageal varices. The varices apparently were the cause of death.

Bacillary Dysentery.—Four patients were treated; in two the etiologic agent was Shigella somnei, and in the other two it was Shigella flexneri. By the fifth day

of oral therapy the clinical symptoms had abated and the stools were free of pathogens in every case. An infant with fever and diarrhea was treated with tetracycline because of the presence of Pseudomonas aeruginosa in the stool. The stools were free of the organism and the patient was asymptomatic after four days of therapy. In each of these patients stools were cultured following cessation of treatment, and there were no bacteriologic relapses.

Pyoderma.—Two patients with skin lesions infected by staphylococci responded adequately to tetracycline, although the organism persisted in one. The pyoderma of a patient with subacute granulocytic leukemia was not affected by the drug, and the staphylococci persisted. Three children were treated for infectious impetigo, and the response was satisfactory in all. Both Str. pyogenes and M. pyogenes var. aureus were isolated from the skin lesions of the three patients. The streptococci were eradicated, whereas the staphylococci persisted.

Osteomyelitis.—Two children, with involvement of the tibia and left foot, respectively, were treated. M. pyogenes var. aureus was cultured from the lesions of both patients. One was treated for two months, with relief of symptoms and apparent healing of the tibial lesion by roentgenogram. Two days after the tetracycline was stopped, pain, swelling, and tenderness developed at the involved site, and a roentgenogram revealed a fracture. Subsequently, the patient was treated with 2,400,000 units of penicillin a day for 37 days, with excellent healing of the fracture and resolution of the osteomyelitis.

A 5-year-old child was treated for five weeks, with alleviation of the clinical symptoms, and no further staphylococci were cultured after the eighth day of therapy; however, there was no change in the destructive process as visualized by roentgenogram.

Miscellaneous Infections.—One patient with an intra-abdominal abscess, one with a soft tissue wound, one with acute brucellosis, and one with acute pyelonephritis were given tetracycline, and all but the first responded satisfactorily. In this patient, the abscess, from which M. pyogenes var. aureus was cultured, was complicated by acute peritonitis and had developed as a hospital infection following hysterectomy. After three days of treatment with tetracycline there was no apparent response. Tetracycline administration was discontinued, and 2,400,000 units of penicillin and 2 gm. of streptomycin a day were given, again without effect upon the course of the disease. The patient died eight days after admission, and the cultures obtained previous to death were positive for the antibiotic-resistant Staphylococcus.

A 20-year-old woman with acute pyelonephritis was admitted in severe distress. Upon admission the rectal temperature was 105 F. On the third day of tetracycline therapy the temperature fell to normal and remained so. Admission cultures of the urine grew many paracolon organisms, Ps. aeruginosa, and a nonhemolytic Streptococcus. At discharge, only the Streptococcus could be cultured.

Brucella suis was cultured from the blood of a 24-year-old man admitted with a temperature of 106 F. No further blood cultures were positive for the organism after initiation of tetracycline therapy, and the patient was asymptomatic by the fifth day of treatment. There has been no recurrence in the seven months which have intervened since therapy.

Asymptomatic Carriers.—Str. pyogenes was cultured from the throat of two patients, and Diplococcus pneumoniae was cultured from an additional two. A three-day course of tetracycline by mouth eradicated the pathogens in all four patients. Corynebacterium diphtheriae was isolated from the nose and throat of another patient. Previous therapy with penicillin, as well as a course of erythromycin, had failed to eradicate the organism. After three days of treatment with tetracycline, the cultures became, and remained, negative.

ADVERSE SYMPTOMS

Untoward effects due to administration of tetracycline were noted for the entire group of 184 patients (Table 2). When given intravenously, in a concentration of not more than 10 mg. per milliliter at a rate no faster than 500 mg. during a 10-minute interval, the drug was well tolerated, except for an occasional complaint of a local burning sensation. Localized swelling, pain, and redness occurred occasionally, and frank thrombophlebitis developed in nine of the patients after several days of intravenous therapy. The local reactions were of no greater magnitude, however, than are those associated with the other tetracyclines.

TABLE 2.—*Adverse Effects Associated with Tetracycline Therapy Occurring in 184 Patients*

Adverse Effect	Route of Administration	Adverse Effect, No. of Cases	
		Definite	Possible
Diarrhea	Oral	5 *	7
Oral moniliasis	Oral	1	..
Nausea and vomiting	Oral	5	17
Nausea and vomiting	I.V.	2	1
Subjective burning, site of injection	I.V.	Frequent	..
Objective local reaction, mild	I.V.	Occasional	..
Marked local reaction (thrombophlebitis)	I.V.	9	..

* Tetracycline administration was discontinued in one case because of diarrhea.

Oral administration of tetracycline had to be discontinued because of an undesirable reaction in only one patient. The drug was stopped because of a persistent diarrhea, which was attributed to it. Tetracycline was the probable cause of diarrhea in an additional four patients and a suspected cause in seven.

Emesis, frequently associated with nausea, occurred in 24 patients, including two patients who were receiving the drug intravenously. Of the 24, there were 12 patients with pertussis, and in these patients emesis typically occurred either with paroxysms of coughing or immediately following feedings. Since tetracycline was given with the feedings, it was not possible to determine whether it was the cause of the emesis. In eight patients nausea and vomiting occurred following oral medication for the first few days of therapy and then subsided. In four of these patients nausea and vomiting were present before antibiotic therapy was begun. In two of the patients tetracycline therapy was stopped for a day because of repeated vomiting following its administration. The drug was given with feedings; consequently emesis could not be definitely attributed to the tetracycline. Vomiting did not return when the drug was again administered, after a lapse of one day. Emesis immediately followed intravenous administration in two patients, although there was no difficulty after subsequent intravenous doses. In no patient was emesis severe enough to require permanent cessation of tetracycline therapy.

As has been mentioned, one patient developed oral moniliasis after receiving the drug for one week.

Serum Concentrations of Tetracycline.—The concentration of tetracycline was determined on 121 specimens of serum, obtained from 73 patients (Tables 3 and 4). Fifteen specimens were from patients who were receiving intravenous therapy, and 106 were from patients who were given the drug orally. Sera were obtained 6, 18, 36, and 48 hours after the initiation of therapy, always just before the succeeding dose. Nine sera were obtained from patients after one week of oral administration of tetracycline.

TABLE 3.—*Serum Concentration of Tetracycline During Oral Therapy* *

	Serum Concentration, γ/Ml.								
	0.16	0.16	0.31	0.63	1.25	2.5	5.0	10	20
Hours After Initial Dose †									
6	4	..	5	10	11	19	4	..	1
18	..	..	1	2	1	4	..	..	..
36	1	1	1	3	7	4	3	2	..
48	..	..	1	3	3	5	..	1	..
7 days	..	..	..	2	4	2	1	..	..
Total determinations	5	1	8	20	26	34	8	3	1

* Adults received an initial dose of 1 gm., followed by 500 mg. every six hours. Children received an initial dose of 25 mg. per kilogram of body weight, followed by 12.5 mg. per kilogram of body weight every six hours.

† Serum was always obtained immediately before the succeeding dose.

TABLE 4.—*Serum Concentration of Tetracycline During Intravenous Therapy with 500 Mg. Every Six Hours*

	Serum Concentration, γ/Ml.				
	2.5	5.0	10	20	40 *
Hours After Initial Dose					
6	1	4	2	2	1
18	..	..	1	..	..
36	1	1	..	..	..
48	1	2	..	..	..
Total determinations	3	7	3	2	1

* This specimen was obtained from the patient who died with purulent meningitis due to a paracolon organism. The patient was oliguric and in shock, requiring arterenol for maintenance of blood pressure from admission to death. Seventy-two hours after the beginning of tetracycline therapy the serum concentration was 40 γ per milliliter and the cerebrospinal fluid concentration was 20 γ per milliliter. On the fourth day of intravenous therapy the serum concentration was over 80 γ per milliliter.

The determinations were performed by the serial two-fold tube-dilution method, with Bacillus cereus as the test organism. The sera were either tested immediately or after refrigeration at a temperature of —20 C. for not more than three days. No deterioration of the tetracycline was noted under these conditions. As has been noted by previous investigators,† the serum concentrations following either intravenous or oral tetracycline administration tended to be slightly higher than those of chlortetracycline under similar circumstances.

Results of Cultures Taken Before and After Treatment with Tetracycline.—The effect of tetracycline on the pathogenic or potentially pathogenic bacteria that

† References 7, 8, and 11.

were associated with the various diseases was determined in 95 cases (Table 5). Only those cases in which cultures were made before and after the beginning of therapy are included. It is noteworthy that 40 cultures of M. pyogenes var. aureus were isolated from the upper respiratory tract after therapy, whereas the organism was cultured only six times previous to therapy. This is in contrast to the findings in 35 patients from whom Str. pyogenes was isolated prior to the initiation of tetracycline therapy, from none of whom Str. pyogenes could be recovered subsequent to treatment. Among the Gram-negative bacteria, there was a tendency for Proteus, Pseudomonas, and some of the coliform organisms either to persist or to be acquired after therapy.

TABLE 5.—*Pathogenic and Potentially Pathogenic Bacteria Cultured from Ninety-Five Patients Before and After Treatment with Tetracycline*

Organisms	Source *	Number Cultured	
		Before Therapy	After Therapy
Micrococcus pyogenes var aureus	U.R.T.	6	40
	Skin	6	5
	Bone	1	0
	Intraperitoneal abscess	1	1
Streptococcus pyogenes	U.R.T.	35	0
	Skin	3	0
Diplococcus pneumoniae	U.R.T.	18	0
	Blood	1	0
Corynebacterium diphtheriae	U.R.T.	1	0
Hemophilus influenzae	C.S.F.	6	1 †
	Blood	2	0
	U.R.T.	2	0
Neisseria meningitidis	C.S.F.	3	0
	Blood	1	0
Proteus species	U.R.T.	0	1
	Stool	2	5
	Urine	1	3
	C.S.F.	1	1
Pseudomonas aeruginosa	U.R.T.	2	2
	Stool	1	0
	Urine	2	1
Coliform bacilli ‡	U.R.T.	4	1
	Urine	3	2
Paracolon bacteria	Urine	2	1
	C.S.F.	1	0
Shigellae species	Stool	4	0
Brucella suis	Blood	1	0
Bacteroides species	C.S.F.	1	0
	Pleural fluid	1	0

* U.R.T., upper respiratory tract; C.S.F., cerebrospinal fluid.
† Patient died 12 hours after onset of therapy.
‡ Includes E. coli, A. aerogenes, and intermediate colon bacilli.

Sensitivity of M. Pyogenes Var. Aureus to Tetracycline and Other Antibiotics.—Previous studies have indicated a close correlation between the concentrations of tetracycline and those of chlortetracycline required to inhibit staphylococci in vitro.‡ The sensitivities of 88 strains of M. pyogenes var. aureus to tetracycline, erythromycin, and penicillin were determined (Fig. 3). Nineteen per cent of the strains were inhibited by 7.8 γ per milliliter, or less, of tetracycline, compared with 22% and 63% inhibited by penicillin and erythromycin, respectively. There was a wide range in the concentration of erythromycin required to inhibit the staphylococcal strains; 55 strains were inhibited by less than 7.8 γ per milliliter, whereas 30 strains were not

‡ References 7 and 8.

inhibited by 250 γ per milliliter. Only three strains were in the intermediate ranges. Erythromycin has purposely been used sparingly in one of the hospitals from which these data was obtained; hence there has been less opportunity for the development of resistant "hospital strains."[22] Although tetracycline has only recently been introduced, its analogues, chlortetracycline and oxytetracycline, have been employed continuously for several years. In a previous study, done at the Municipal Contagious Disease Hospital,[12] only 18.4% of 76 staphylococcal strains cultured at discharge were inhibited by 9.9 γ or less of chlortetracycline. This figure is comparable to the 18% that were found to be inhibited by 7.8 γ per milliliter or less of tetracycline in this study.

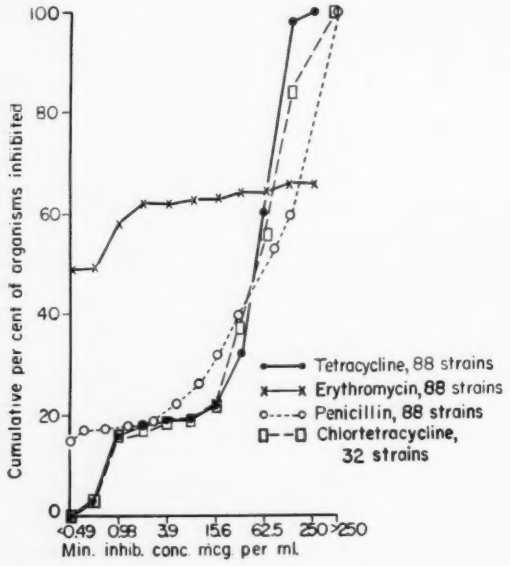

Fig.3.—Minimum concentration of tetracycline, chlortetracycline, erythromycin, and penicillin required to inhibit Micrococcus pyogenes var. aureus.

We studied the comparative effects of tetracycline and chlortetracycline on 32 strains of M. pyogenes var. aureus. The similarity of the minimal inhibitory concentrations of these two drugs is shown in Figure 3. There was a two-tube variation between them in 6.2% of the strains and a one-tube variation in 50%; the minimal inhibitory concentrations were the same in the remaining 43.8%.

COMMENT

The effect of tetracycline upon the 153 patients studied by us gives further evidence as to the similarity of the antibacterial activity of analogues.

If this new compound is as well absorbed as the other tetracyclines, it should be found in higher concentration in the serum, because of its greater stability at body temperature.[5] Higher serum concentrations have been observed by Finland and his associates [8] and by us. Furthermore, three of us [11] have shown that penetra-

tion of tetracycline into the cerebrospinal fluid is more constant and that the mean concentration as well as the range of concentrations of tetracycline is higher than is true of either chlortetracycline or oxytetracycline.

In the light of these observations, one would expect tetracycline to be at least as effective as its analogues. The present report verifies this supposition. We have obtained excellent results with tetracycline in the treatment of pneumococcic and hemolytic streptococcic infections. The response in pertussis was comparable to that obtained in the same hospital with chlortetracycline and oxytetracycline. Of the eight unsatisfactory responses in the 153 patients treated, significant complications were associated in four, and in three additional patients the causative agents were staphylococci resistant to high concentrations of tetracycline.

While the number of cases of meningitis, bacillary dysentery, brucellosis, pyoderma, infectious impetigo, and pyelonephritis are small, the satisfactory outcome in these cases makes it appear that tetracycline may be as effective as its analogues in these conditions.

Although the response to tetracycline in four patients with meningitis caused by H. influenzae was as good as has been reported with therapy with any of the available antibiotics, the results in two other patients were difficult to evaluate. One patient was admitted in a moribund state, and in the case of the other the administration of tetracycline was discontinued prematurely. Complications were likewise responsible for the death of a patient with meningitis caused by a paracolon organism. The one patient with meningitis in whom therapy with tetracycline definitely failed had meningitis caused by a Proteus organism. In our experience, Proteus infections are seldom affected by the tetracyclines. In fact, Proteus is likely to replace other bacteria when a patient is receiving one of the tetracyclines (Table 5).

Further studies will be necessary to determine whether tetracycline will consistently eradicate the diphtheria bacillus from carriers. In vitro studies by English and co-workers showed a strain of C. diphtheriae to be relatively resistant to tetracycline.[5]

Our clinical results have been supported by a study of the disappearance of the offending micro-organisms from the skin, stool, and body fluids of patients treated with tetracycline. Except for staphylococci, most of the Gram-positive cocci disappeared, while Proteus and Pseudomonas organisms tended to appear under treatment, and some of the coliform organisms remained. The acquisition of strains of M. pyogenes var. aureus in the nose and throat of patients after admission to the hospital has previously been reported.[12] The failure to eradicate the Proteus and Pseudomonas species is consistent with the results of in vitro studies of previous investigators.§

Although tetracycline appears to be at least as potent a therapeutic weapon as its analogues, a much larger number of cases will be required to demonstrate a definite therapeutic superiority, should such exist. Although nausea, vomiting, or diarrhea did follow its administration in a few patients, the incidence was low. This is demonstrated by the fact that in only one instance was it necessary to stop the administration of tetracycline because of a side-reaction, diarrhea. A local inflammatory process was not infrequently associated with the intravenous administration

§ References 5 and 8.

of the tetracycline, progressing to thrombophlebitis in nine patients. In nearly all these cases, however, an indwelling plastic catheter was used to administer the drug and intravenous fluids. The incidence was no greater than that which we have observed with chlortetracycline and oxytetracycline.

SUMMARY

Tetracycline was administered to 184 patients with acute infections. The antibiotic was found to be clinically as effective as oxytetracycline and chlortetracycline in the 153 patients evaluated. The results were satisfactory in 40 patients with acute streptococcic infections, 24 patients with pertussis, and 25 patients with pneumonia. Among 16 patients with acute purulent meningitis, the clinical response was similar to that expected under established therapeutic regimens. Four patients with Shigella dysentary and one patient with acute brucellosis, one with acute pyelonephritis caused by a paracolon bacillus, and one with empyema caused by Bacteroides were successfully treated. Unsatisfactory responses were observed in eight patients, in three of whom the primary disease was caused by an antibiotic-resistant Staphylococcus. Of the remaining five cases, two may be regarded as bacteriologic failures.

Adverse symptoms, mainly gastrointestinal, due to the administration of tetracycline, were minimal. Diarrhea was attributed to the drug in five instances, and emesis occurred in an equal number of patients.

The serum concentrations of tetracycline were determined 6 to 48 hours after administration of the drug by both the oral and the intravenous route. The adults treated orally were given an initial dose of 1 gm., followed by 500 mg. every six hours. Children were given 25 mg. per kilogram of body weight initially, followed by 12.5 mg. per kilogram of body weight every six hours. With this dose schedule, the serum concentrations ranged from 0.63 to 2.5 γ per milliliter in 75% of 106 specimens. The concentrations following intravenous doses of the same amount, except that no initial doses were given, ranged from 2.5 to 40 γ per milliliter.

The antibacterial spectrum of tetracycline, as determined clinically, was found to be similar to that of chlortetracycline and oxytetracycline. Also, the in vitro inhibition of 32 strains of Micrococcus pyogenes var. aureus by tetracycline paralleled that of chlortetracycline. There was a tendency for staphylococci, coliform bacilli, Pseudomonas aeruginosa, and Proteus species to persist or appear following the initiation of tetracycline therapy.

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SUBACUTE EROSIVE ("PEPTIC") ESOPHAGITIS

Clinical Study of One Hundred Cases

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IT IS NOT surprising that there has been increasing awareness of the frequency of esophagitis with the internist's adoption of diagnostic esophagoscopy as his own procedure. Detection of esophagitis by "medical esophagoscopy," a technique which has become as simple and safe as gastroscopy, has helped explain for him the cause of several puzzling chest and upper abdominal problems, such as certain bizarre "cardiac" symptoms, some cases of hematemesis, dysphagia of the puerperium, and unexpectedly severe symptoms associated with hiatus hernia.

Classification of esophagitis is made difficult by the fact that, like other organs, the esophagus has its own established pattern of reacting to adverse influence, and the specific nature of the influence is not the main factor controlling tissue response. The result is that objective findings may be quite similar among patients with varying clinical pictures. The present communication deals with subacute erosive esophagitis, also known as "peptic" and "regurgitant" esophagitis. This, together with its more acute counterpart, acute erosive esophagitis, appears to be the commonest disease of the esophagus. The distinction between the acute and the subacute is largely theoretical. It is important to note that in the cases under discussion there was no specific etiologic factor at work, such as specific infectious agent, ingestion of a corrosive, recent retention of indwelling eosophageal tube, systemic infectious disease, cerebral disease or important cutaneous trauma (Cushing and Curling influence), obstruction at the cardia, carcinoma of the esophagus, diffuse collagen disease, or deficiency disease.

MATERIAL

One hundred personally observed adults with the esophagoscopic and/or transesophagoscopic biopsy diagnosis of subacute erosive esophagitis were studied. Esophageal investigation was instituted because of chest or upper abdominal symptoms, upper gastrointestinal hemorrhage, or because the presence of cirrhosis necessitated search for esophageal varices. There were 22 women and 5 Negroes in the group. At the time the diagnosis of esophagitis was first established, the number of patients per age-decade from the second through the ninth was, respectively, 4, 22, 19, 16, 12, 17, 7, and 3.

The patients were discharged with a variety of diagnoses other than esophagitis and the diseases believed to be causally associated with esophagitis. Those that appeared to be unrelated to the esophageal disease included portal cirrhosis (14 patients), chronic hepatitis (3), diabetes (3), hemochromatosis (1), cholelithiasis (5), hypochondriasis (1), muscular dystrophy (1), pulmonary tuberculosis (1), and diverticulosis coli (4).

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METHODS

The esophagoscopic evaluations were made under four-diameter magnification (Eder-Hufford esophagoscope). Sixty-four patients were examined more than once, and 14 were reexamined at close intervals over periods of from 7 to 12 months. Transesophagoscopic biopsy specimens were taken from most but will not be described at this time except as they aided diagnosis. There were no complications to the biopsy procedure.

Swallowing time[1] was measured as the interval between initiation of deglutition and emptying of the esophageal ampulla. This is determined by the ancient method of timing from the moment of elevation of the larynx to the appearance of the second swallowing sound (Durchpressgeräusch) just below the xiphoid. Lukewarm water is used for the bolus. The second swallowing sound is heard through the stethoscope as a distinct gurgling, caused by the air-liquid mixture passing from the ampulla into the stomach. The normal swallowing time, as measured by this method,[1] is four to seven seconds, but it is important to understand that the method is a crude one. It is a screening test which depends on lack of specificity for its special value.

For gastric analysis, a two and one-half hour test with 0.36 mg. histamine base for stimulation was used. The roentgenologic studies were made by several staff radiologists at three university-affiliated hospitals.

SYMPTOMATIC PICTURE

The esophagitis of 13 patients was subclinical and was discovered upon esophagoscopy performed for other reasons: in a routine search for varices in nine persons with cirrhosis, to elucidate abnormality incidentally found upon x-ray examination of two ulcer patients, and during routine upper gastrointestinal survey of two patients. Because of unrelated concomitant disease, the significance of symptoms in five additional patients could not be judged.

The first symptom in 11 patients was hematemesis, as will be described. Three later developed dysphagia, but the other eight had no manifestation other than the bleeding, which in four patients was repeated over intervals of from 4 to 14 months.

The complaints of the other patients were such that they could be classified easily into one of four symptom complexes. Although, of course, during the study many patients with esophagitis-like symptoms had been examined and found to have no esophageal disease, the patients who had esophagitis had rather characteristic complaints. The influence of complications and aggravating factors over the clinical picture was not particularly striking. Thus, the presence of esophageal stricture could not always be predicted from the severity of the obstructive symptoms; nor did the complaints of patients with hiatus hernia necessarily vary from those with a competent hiatus.

Twenty-nine patients complained of dysphagia and little else. The only discomfort was that which accompanied temporary arrest of food within the esophagus. Characteristically the patient could describe his sensations in great detail and was particularly aware of the exact level of the esophagus which gave him trouble. The sense of obstruction was regularly felt somewhere between the level of the midmanubrium and the xiphoid. Usually solid dry foods were more difficult to swallow than liquids, but a few patients described peculiar individual idiosyncrasies. Thus, one could drink milk with ease but could hardly get water past the midesophagus. Another could drink iced tea but had trouble with hot tea.

Six patients complained of dysphagia, as just described, but in addition regularly experienced important substernal pain with each swallow.

In nine patients there was dysphagia without pain, but nocturnal pyrosis and brief episodes of squeezing substernal pain at odd intervals were prominent.

Twenty-seven patients had no complaints referable to deglutition. Their problem was burning or aching deep substernal pain. Characteristically this began about a half-hour after meals and persisted a couple of hours at a time. Intensification upon recumbency was occasionally noted by most of the patients. Several mentioned belching as the main aggravating circumstance. Food did not afford relief; nor did it aggravate the pain, in most. In general, the pain was characterized by its unpredictable chronologic pattern. One patient had on several occasions discovered blood and gastric contents on the pillow-case upon waking in the morning.

The patients who had complaints believed to be due to esophagitis described courses which were notably static, with little spontaneous fluctuation in the intensity of symptoms or general incapacity. Eleven vomited blood as the first sign of illness. The duration of symptoms at the time of study among the others was as follows: 1 week, 2 patients; 2 to 4 weeks, 9 patients; 5 to 8 weeks, 15 patients; 2 to 6 months, 15 patients; 7 to 12 months, 6 patients; 1 to 2 years, 6 patients; 3 to 4 years, 9 patients; 5 to 10 years, 6 patients; 20 years, 2 patients; 47 years, 1 patient.

AGGRAVATING CONDITIONS AND OTHER DISEASES PERHAPS RELATED TO ESOPHAGITIS

The etiology of esophagitis is not clear, but, if acid-pepsin activity of refluxed gastric contents should be important, several patients had diseases which can be considered as aggravating factors.

There was hiatus hernia in 24 patients; the total number of patients with hiatus hernia examined esophagoscopically during the study period was 104. Thirteen patients gave a history of frequent vomiting antedating esophageal symptoms. Five, now in the puerperium or long post partum, had had pernicious vomiting of pregnancy,[2] and a sixth, in the fifth month of pregnancy at the time of study, had had rather severe morning sickness during the first trimester. One elderly man had chronic partial pyloric obstruction and had vomited on an average of about once a day for a year. Three patients had had severe vomiting for several days following abdominal surgery under general anesthesia, the esophagoscopic examinations having been made shortly after these episodes.

At the time the esophagitis was first diagnosed, seven patients had an active duodenal ulcer, four had an inactive duodenal ulcer, and three had an active gastric ulcer. On the other hand, eight patients had had gastric surgery, either for the purpose of or incidentally resulting in reduction of gastric acidity. There had been three subtotal gastrectomies and two subdiaphragmatic vagotomies and gastroenterostomies for treatment of duodenal ulcer. Two patients had had total gastrectomy for ulcer high on the gastric lesser curvature. The eighth patient had had an emergency partial esophagogastrectomy 18 months previously for bleeding esophageal varices.

Other stomach diseases included carcinoma in two instances, leiomyosarcoma in one, retained foreign body which had quickly traversed the esophagus in one, prolapse of the gastric mucosa into the duodenal bulb in three, prolapse of the gastric mucosa into the esophageal ampulla in one, and chronic atrophic gastritis in five.

An esophageal diverticulum was present in six patients. Four of these were mid-esophageal, and two were situated above the area of esophagitis. The other two and an epiphrenic diverticulum were located within the segment involved by esophagitis.

RESULTS OF DIAGNOSTIC PROCEDURES

Swallowing Time.—Measurements of the swallowing time of 35 patients who had no esophageal or cardial disease other than the esophagitis demonstrated three types of abnormal pattern. Because this is a crude test, no conclusions could be drawn other than that abnormality had been suggested by clinical examination. In

Fig. 1.—Roentgenologic appearance in a case of subacute erosive esophagitis without ulcer or stricture. Muscular irritability with distortion of the mucosal pattern is the important change.

four patients no swallowing sounds could be heard, in spite of many attempts over several days. In 20 patients the sounds came through with the usual partial regularity, but the time was always prolonged in excess of 12 seconds (normal, approximately 7 seconds). In eight instances the irregularity of the transit time from day to day seemed in excess of normal. The other three patients had normal swallowing times upon repeated examinations. It appeared that the general usefulness of this simple clinical test had been demonstrated, although it is important to add that abnormal swallowing time is not rare in normal subjects.

Gastric Analysis.—Among 52 patients whose capacity to secrete acid in response to histamine was tested, no free acid could be elicited in 11. The others showed secretory ranges within normal limits.

X-Ray Findings.—The patients were studied roentgenologically by several examiners. The diagnosis of esophagitis was made in only six instances (Fig. 1). Carcinoma of the esophagus was questioned in four others but later disproved, and in three the esophagitis was misinterpreted as varices.

On the other hand, the radiologic method proved more helpful than the endoscopic method in elucidating the extent of secondary stricture formation and in detecting the esophageal diverticula. Only two of the six diverticula could be found by esophagoscopy, in spite of the fact that their presence was already known.

Esophagoscopic Findings.—The first examination, prior to treatment, showed that the esophagitis involved the entire organ in 3 patients, the distal three-quarters

Fig. 2.—Esophagoscopic findings in subacute erosive esophagitis: hyperemia, exudate, and erosions. In this patient many of the erosions were exuding tiny drops of blood.

in 3, the distal two-thirds in 6, the distal one-half in 19, the distal one-third in 30, the distal one-quarter in 21, and the distal one-sixth in 14. The first esophagoscopic examination in four patients was believed to be normal, but biopsy of the normal-appearing mucosa revealed the histopathologic picture of esophagitis. It seems particularly significant that the esophagitis was always contiguous with the esophagogastric junction. Frequently the disease was patchy in distribution and severest proximally, but always the segment close to the stomach was involved.

There were three features of the endoscopic picture which were found with some regularity: hyperemia, erosions, and exudate (Fig. 2). Usually the whole diseased area was hyperemic. A deep scarlet appearance was occasionally found,

but more often the intensity of redness was not striking. Edema, when present, was regularly mild, and the affected areas were scattered. Rarely was segmental spasm apparent esophagoscopically.

It had been suspected prior to the study that esophageal erosions are frequently overlooked at esophagoscopy, even under four-diameter magnification. For a period, patients coming to esophagoscopy were given a drink of fluorescein immediately before they were examined in order to stain eroded areas. Then it was found that erosions are common in subacute esophagitis—so much so that the term "erosive" has been added in the morphologic classification. After this experience, closer scrutiny under magnification has permitted identification of at least a few erosions in every patient with this disease. In some cases erosions were found to be present in great numbers over all of the diseased area. The configuration of the individual lesions was circular or oval. Direct mensuration showed the usual diameter to be approximately 2 mm. Occasionally very large denuded areas were found, usually close to the esophagogastric junction. Biopsy on numerous occasions proved that the lesions extended only about two-thirds of the way through the epithelial layer. This was true even of those erosions which were exuding blood, the explanation being that the vessels of the rete pegs were exposed thereby. The result of serial examinations left the impression that erosions may heal or at least improve to the point of becoming undetectable within a period of a few days.

Interpretation of exudate overlying the mucosa is usually a difficult matter for the esophagoscopist. Refluxed gastric contents are easily identified, but swallowed material is a different problem. The exudate of esophagitis is regularly of small amount, never contains bubbles, is white or light gray, and is closely applied to the mucosa. Ordinarily just a skim of translucent nacreous material is found over the surface, and this is easily scraped away with the rounded tip of the esophagoscope. When examined microscopically, both fresh and after fixation and sectioning, the material is found to consist largely of desquamated epithelial cells, with few pus cells and little mucus.

COMPLICATIONS OF ESOPHAGITIS

Twelve patients who were esophagoscoped during active hematemesis were found to be bleeding from esophagitis. The bleeding in four cases was very severe, necessitating emergency partial esophagogastrectomy. Transesophagoscopic packing with oxycel around an indwelling Levin tube was used in four cases, and, even though each patient ejected the plug within a few hours, none bled further at that time. Pneumatic tamponade proved to be moderately satisfactory in controlling hemorrhage in the other patients.

Seven of 22 other bleeders with esophagitis were studied shortly after hemorrhage had ceased, and, as a result of the esophagoscopic findings plus absence of demonstrable abnormality elsewhere in the upper gastrointestinal tract, it was concluded that the esophagitis had been responsible. Among the 19 patients proved or believed to have hemorrhaged from esophagitis, there were five who gave a history of at least one episode of hematemesis in the past.

There were 15 other bleeders in whom esophagitis could not be primarily blamed. Of most interest among these were patients with esophageal varices secondary to cirrhosis. Altogether there were varices in 14, and each gave a history of hemateme-

sis, a most significant observation. Three were examined esophagoscopically during hemorrhage, and all were proved to be bleeding from the varices. It was concluded that an important role had to be ascribed to the esophagitis in initiating disruption of the varices in these cases.

There was a chronic stricture in the area of esophagitis in 11 instances (Fig. 3). In each there was only one stricture, and in all but one it was within 5 cm. of the esophagogastric junction. The stricture was midesophageal in the other. All cases were treated satisfactorily by transoral dilatations, but a long course was found necessary in each.

Fig. 3.—Moderate stricture secondary to esophagitis, in a patient with small hiatus hernia. Dilatations were successful in opening the stricture.

There was an esophageal ulcer in seven patients. The relationship between esophageal ulcer and esophagitis is not at all clear, and there is no convincing reason for listing one as a complication of the other. Rather regularly there is a small amount of inflammation surrounding esophageal ulcers, but this is a matter different from the diffuse esophagitis which is under discussion. During the period of study, a total of 17 cases of esophageal ulcer were diagnosed. Thus, the combination of esophagitis and ulcer seemed significantly common.

Only one patient gave a history of chronic pulmonary disease, suggesting recurrent nocturnal aspiration of regurgitated gastric material (Fig. 4). There was no hiatus hernia, stricture, or diverticulum. The patient had had symptoms suggestive of esophagitis for four years, marked particularly by nocturnal sub-

sternal pain. During this period there had been seven documented episodes of pneumonia. The chest studies showed severe pulmonary fibrosis through both lung fields.

RESULTS OF TREATMENT

Treatment of esophagitis has for years been based on the assumption that the disease is at least in part secondary to corrosive action of refluxing gastric contents.* Consequently, antacids have become a standard prescription. The symptom of heartburn has encouraged use of antispasmodics. For many years the astrigent and mild antacid properties of bismuth subnitrate and bismuth subcarbonate powder have been found particularly efficacious. The former salt has, however, been dropped in favor of the latter, because of certain toxic properties. Symptomatic relief has generally been satisfactory, although objective proof of benefit has been rather fragmentary.

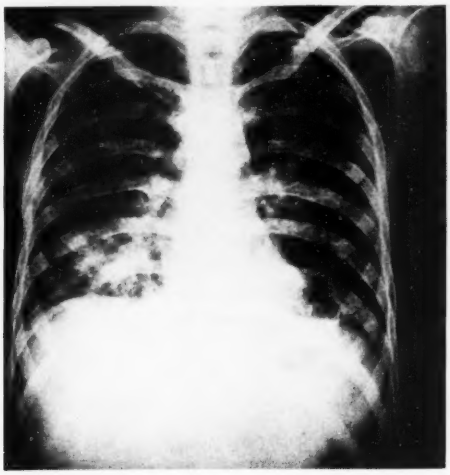

Fig. 4.—Extensive pulmonary fibrosis secondary to repeated bouts of aspiration pneumonia in a patient with esophagitis. There was no other esophageal disease.

In the present series an effort was made to evaluate objectively the results of treatment in those patients who did not have local aggravating disease, had developed no stricture, and had no complication which required local manipulation. This eliminated, in particular, patients with hiatus hernia. Thirty of the 64 patients who were reexamined esophagoscopically following initiation of therapy remained for evaluation, and 95 esophagoscopic examinations were made of these. The repeated examinations were made at various intervals. During the interims the patients followed one of three prescribed regimens. One group was given no treatment at all, and the patients were advised that time alone was indicated. The second regimen consisted of a bland diet, belladonna tincture to tolerance one-half hour before each meal, 16 ml. of aluminum hydroxide gel seven times a day

* References 3-13.

during waking hours, interdiction of tobacco and alcohol, and elevation of the head of the bed 10 in. (25 cm.). The third regimen consisted only of bismuth subcarbonate, one-half hour after every meal and at bed time, taken in 2 gm. doses either as the dry powder or in a thick paste. In general, the purpose was to compare the results of a moderately strict ambulatory ulcer regimen with simple local therapy and no prescribed therapy at all.

Subjectively, all the patients receiving active treatment were helped to some extent. The relief was often short-lived, so that symptoms returned before the next dose of medicine was due. Some of the treated patients were rendered asymptomatic and had no further trouble. The same was observed among the untreated group, and it was quite apparent that in many instances the esophagitis was a self-limited disease.

Objective Changes upon 65 Repeat Esophagoscopic Examinations During Three Therapy Regimens (30 Patients)

Interval Between Examinations	Regimen	Patients, No.	Observation			
			Worse	No Change	Better	Cure
Less than 1 wk	No therapy	3	..	2	1	..
	Ulcer therapy	5	..	2	2	1
	Bi subcarb	5	1	3	..	1
1-2 wk	No therapy	6	2	3	1	..
	Ulcer therapy	4	..	4	..	..
	Bi subcarb	5	..	2	3	..
3-6 wk	No therapy	3	1	..	..	2
	Ulcer therapy	7	1	3	..	3
	Bi subcarb	10	1	1	7	1
7-12 wk	No therapy	4	1	3	..	..
	Ulcer therapy	3	..	1	1	1
	Bi subcarb	2	..	..	..	2
4-6 mo	No therapy	4	1	..	..	3
	Ulcer therapy	1	..	..	..	1
	Bi subcarb	3	..	..	2	1

Objective evaluation of treatment, as judged upon repeat esophagoscopic examination, is outlined in the Table. It is seen that there was no important difference in objective response between the three groups. Some of this is believed to be explained by the apparent self-limited nature of some cases of esophagitis. Spontaneous clearing occurred during the period of observation in five of nine patients who were not actively treated. The esophagus of two patients had returned to normal within a week of the first examination and initiation of treatment, but the disease in both returned at a later date in spite of continued therapy.

COMMENT

The cases for the present study were selected and grouped together on the basis of the morphologic appearance presented by the pathologic process, regardless of apparent etiology. Certain reports on esophagitis have been based on common assumed etiologic circumstances, such as coexisting "peptic" ulcer, thus suggest-

ing the etiology of the esophagitis through selection of case material. It seems best to start with the pathology, letting the chips fall where they may as far as etiology is concerned.

The circumstantial clinical evidence points directly at acid-peptic corrosion secondary to transcardial reflux as the cause of the disease.† The frequency with which esophagitis occurs with hiatus hernia, pregnancy, and prolonged vomiting suggests an association with cardial incompetence which is more than coincidental. Furthermore, there is a significant frequency of association with gastric and duodenal ulcer, and the esophageal disease always extends proximally from the esophagogastric junction. It is for these reasons that the terms "peptic" and "regurgitant" have been applied to this form of esophagitis.

There are, however, some disquieting facts to be faced if the etiology is peptic corrosion. As demonstrated in the present study, achlorhydria is not infrequently encountered in these patients. At times, the esophageal troubles begin only following surgical procedures which are specifically designed to reduce acid production, including total gastrectomy. In the present series it was clear that medical efforts to control gastric acidity and to discourage nocturnal regurgitation had no specific effect on the gross morphologic evidence of disease.

Perhaps even more disturbing is the histopathologic picture which is found upon biopsy of subacute erosive esophagitis. This picture, the details of which will be reported at another time, consistently shows an epithelial layer which is normal except for superficial erosions. The erosions are characterized by absence of inflammation. The submucosa, on the other hand, is striking because of the regularity with which it is involved by inflammatory infiltrate. In other words, histopathologically the disease is submucosal, not on the surface. It is as though the noxious influence is working under the mucosa and that surface erosion might be secondary to underlying disease.

SUMMARY AND CONCLUSIONS

One hundred cases with the morphologic diagnosis of subacute erosive esophagitis are reported, with emphasis on esophagoscopic appearances, associated upper gastrointestinal disease and possible etiologic circumstances, symptomatic pictures, complications, and results of treatment.

It is concluded that subacute erosive esophagitis is a disease of considerable frequency and of serious potential clinical importance. The facts do not permit unreserved acceptance of acid-peptic corrosion as the cause.

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HISTIOCYTIC MEDULLARY RETICULOSIS

Report of Two Cases

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SCOTT and Robb-Smith [1] reported four cases of histiocytic medullary reticulosis which presented a definite clinical and pathologic picture. The clinical course is one of a rapidly fatal disease characterized by high irregular fever, wasting of the body, gross splenomegaly and hepatomegaly, and moderate enlargement of the lymph nodes. These patients also develop a rapidly increasing anemia, with leucopenia and thrombocytopenia, hemorrhagic manifestations, and jaundice. Terminally, a necrotizing angina may develop. The pathologic picture shows a proliferation in the lymphoid organs of active phagocytic cells containing nuclear debris and erythrocytes. In addition to the typical histiocytic cells, so-called prohistiocytes are present, and giant forms of these occur. Areas of hemorrhage and necrosis are common. Some of the lymph nodes show compression of the follicle borders by proliferation of their centers. This picture, according to Robb-Smith and others,* is similar histologically to acute reticulosis of children, generally known as Letterer-Siwe syndrome. The two cases we are reporting showed these findings.

REPORT OF CASES

CASE 1.—A 39-year-old Chinese male grocery clerk was admitted to Queen's Hospital on May 21, 1952, with the chief complaint of fever. He stated that three months prior to admission he began having intermittent bouts of fever, usually preceded by a short chill, of 15 to 20 minutes' duration. During these attacks, his temperature rose to 103 to 104 F., usually remaining at this level for four to six hours, and then returned to normal. These episodes were usually followed by night sweats. The attack would occur at varying intervals of 6 to 10 days, but the intervals were getting progressively shorter. Between these episodes he felt reasonably well, although he did experience increased fatigue on exertion.

About one week before admission he developed persistent paroxysms of coughing, productive of a witish sputum. These paroxysms frequently resulted in vomiting.

Physical examination on admission showed a well-nourished Chinese man in no acute distress. The ears, eyes, nose, and throat were normal. The chest was emphysematous in type. No rales were heard. The heart was regular, and no murmurs were heard. The blood pressure was 120/80. The abdomen was obese. The liver edge was felt 2 fingerbreadths below the right costal margin. It was not tender. The extremities were normal. A cursory neurological examination showed no abnormality. The clinical possibilities considered were (1) subicteric hepatitis, (2) pulmonary tuberculosis, and (3) typhoid fever.

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* References 2-5.

Laboratory findings were as follows: Blood studies showed 3,940,000 RBC, 6,250 WBC, and 10.5 gm. of hemoglobin. The differential count showed 58% polymorphonuclear lymphocytes, 7% stab cells, 4% monocytes, and 2% eosinophiles. There was moderate achromia with anisocytosis. Urine analysis showed a specific gravity of 1.014. Tests for albumin and sugar were negative. Agglutination tests for Brucella, Proteus X19, typhoid, and paratyphoid A were negative in all dilutions. A test for paratyphoid B was positive in dilution of 1:60. Three blood cultures made on successive days were negative for organisms. Three stool cultures for the typhoid-dysentery group were negative. Blood studies for the lupus erythematosus phenomenon were negative. Three sputum concentration studies for acid-fast bacilli were negative. Repeated smears for malaria parasites were negative. Three cultures of sputum for pathologic fungi were negative. Anterior-posterior and lateral chest x-rays made on admission and x-rays of excessory nasal sinuses showed no abnormalities.

During the patient's hospital stay his disease ran a febrile course. The temperature in the fever paroxysms fluctuated from 99 to 104 F. daily. During the patient's stay in the hospital all agglutination tests and cultures were repeated several times and were negative. The patient felt reasonably well when his temperature was lower. During this period his weight remained constant. His cough persisted throughout his entire stay. Ear, nose, and throat examination and x-rays of sinuses were normal. Repeated chest x-rays showed no definite change from the original film, taken on admission. The patient remained in the hospital 22 days.

Treatment during this period consisted of 1,000,000 units of penicillin daily with 0.5 gm. of streptomycin parenterally daily for one week, after which it was discontinued. Two hundred fifty milligrams of oxytetracycline (Terramycin) was given orally for 10 days without effect. Five hundred milligrams of chloramphenicol (Chloromycetin) was given orally every six hours for one week, also without effect. He also received symptomatic treatment. The patient went home against advice, on June 11, 1952. He was signed out as having fever of undetermined origin.

He stayed in bed at home after he left the hospital and was definitely unimproved. On July 19, 1952, he was readmitted to Queen's Hospital with the same complaint.

Physical examination on this admission showed a 39-year-old Chinese man who appeared acutely ill. The pupils reacted to light and in accommodation. The eyegrounds showed Grade 2 hypertensive retinopathy with marked angiospasm; no papilledema could be seen. The ears were normal. The right naris was obstructed. The mouth showed a gingivitis with some pyorrhea alveolaris. There was a postnasal mucopurulent drip. The pharyngeal wall had a dirty gray pseudomembrane with many raised areas 1 to 2 cm. in diameter, which appeared to be hypertrophied lymphoid tissue. The neck showed a few shotty lymph nodes in the anterior cervical chain. The chest was clear. The heart was regular. There were no murmurs. The blood pressure was 120/70. The liver was felt 2 fingerbreadths below the right costal margin. The spleen was barely palpable. The genitals were normal. A rectal examination showed no abnormality. The skin showed a morbilliform discoloration over the trunk, with erythematous circular patches 2 cm. in diameter on the neck and arms and legs. A cursory neurological examination showed no abnormalities. The clinical impression on this admission was typhoid, atypical Hodgkin's disease, brucellosis, or aleukemic leukemia.

Laboratory findings were as follows: Complete blood cell count showed 2,910,000 RBC and 2,100 WBC, with 8.5 gm. of hemoglobin. The differential count showed 66% polymorphonuclear leucocytes, 6% lymphocytes, 28% stab cells, and 1% nucleated red cells. There was slight anisocytosis of the red cells. Urine analysis showed a trace of albumin; specific gravity was 1.010. Repeated blood cultures were negative. Stool cultures were again negative for the typhoid-dysentery group. The sedimentation rate was 31 mm. corrected (Wintrobe). Blood chemistry studies showed a urea nitrogen of 11 mg. per 100 cc. The serum chloride was 554 mg. per 100 cc. The CO_2-combining power was 70%. Repeated blood smears for malarial parasites were negative. A sulfobromophthalein (Bromsulphalein) test showed 48% dye retention after 30 minutes. A cold agglutination test overnight at 4 C. was positive in 1:16 dilution. One hour at room temperature showed no agglutination in any dilution. Blood studies for the lupus erythematosus phenomenon were again negative. X-rays made of skull, chest, and nasal accessory sinus; a gastrointestinal x-ray series, and an intravenous pyelogram showed no abnormalities. An electrocardiogram was considered within normal limits.

During the patient's hospital stay he continued to have a spiking temperature, varying from 99.2 to 104 F. The pulse rate varied from 90 to 103 beats per minute and usually kept pace with the temperature. On July 29, 1952, lymph nodes on the left anterior cervical chain were palpable. The spleen also became definitely palpable, and the liver edge seemed more definitely palpable. The patient continued to go downhill rapidly. On July 30, 1952, the patient vomited 200 cc. of digested blood and began developing purpuric spots on the lips, buccal mucosa, and skin. The membrane in the posterior nasopharynx also began to bleed, and gangrenous sloughing developed in the anorectal area.

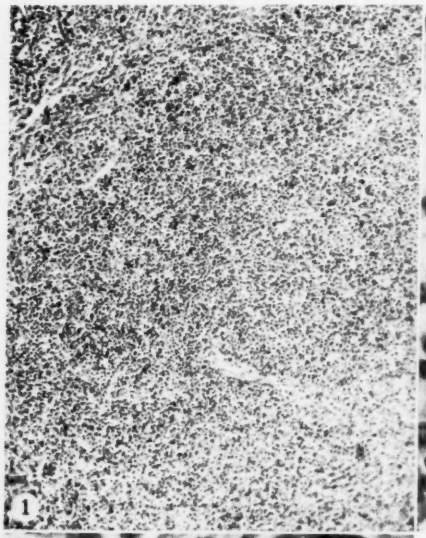
The platelet count at this time was 17,560. The urine began to show a large amount of albumin, with specific gravity of 1.010. The total protein at this time was 3.90 gm. per 100 cc., with 1.47 gm. of globulin and 2.43 gm. of albumin. Serum chloride was 586 mg. per 100 cc., and the CO_2-combining power was 26 vol. %. A repeat platelet count on Aug. 11, 1952, was 34,160. The hemoglobin was 8 gm., and the red blood cells were 4,270,000, with 3,500 WBC. Differential count was 3% juvenile forms, 45% stab cells, 32% segmented cells, and 16% lymphocytes. The purpuric phenomena became progressively worse, and on Aug. 12, 1952, the RBC had fallen to 2,900,000 and platelets to 11,800.

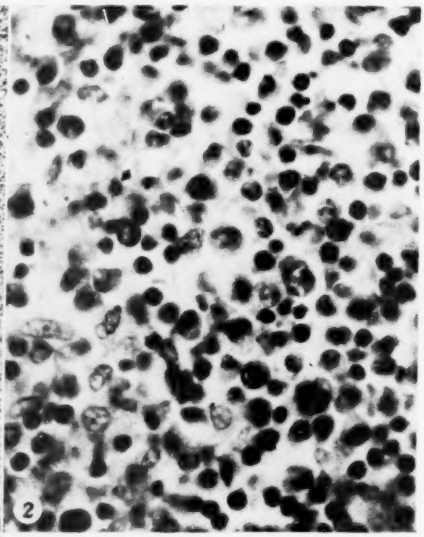
During the patient's stay in the hospital his treatment consisted of corticotropin (ACTH), 50 mg. parenterally four times a day, and a total of 17 transfusions of 500 cc. each of whole blood. In spite of all treatment he went progressively downhill and died on Aug. 12, 1952.

The autopsy showed a poorly nourished 39-year-old Chinese man, showing moderate postmortem lividity and rigidity. The skin showed symmetrical butterfly petechial hemorrhages, most marked on the upper extremities, especially on the forearms; on the pretibial regions, and over the thorax. The tibial regions showed cutaneous ulcerations, 0.5 cm. in diameter, and there was a gangrenous area over the chest and in the anogenital region. The panniculus measured 1.5 cm., and on the abdomen, 2 cm. The right lung weighed 400 gm. The surface was pink to gray. The cut surface showed slight congestion and edema. The left lung weighed 350 gm. and was similar to the right. A few peribronchial nodes, 0.5 cm. in diameter, contained anthracotic deposits. The pericardium was distended with about 800 to 1,000 cc. of dark purplish fluid. The entire precordial surface was covered with a hemorrhagic lining, extending over the entire surface of the heart and over the base of the great vessels. The heart weighed about 250 gm. The myocardium, endocardium, coronary orifices and arteries, valves, and papillary muscles appeared normal. The aorta showed slight atheromatous change. The peritoneum was clean and smooth and without adhesions. About 100 cc. of clear yellowish fluid was present in abdominal cavity. The mesentery and omentum appeared normal. The esophagus, stomach, large and small intestines, and gall bladder appeared normal. The liver weighed 2,710 gm. The inferior edge was rounded and extended 8 cm. below the right costal margin. The edges appeared smooth, and the cut surface showed congestion. The pancreas appeared normal. The spleen weighed 980 gm. The capsule was slightly dull and thickened. It was dark purple throughout except for an infarcted area about 5 cm. in diameter on its posterior edge. The right kidney weighed 310 gm. The capsule stripped fairly easily, leaving a smooth surface containing a few stellate scars. There were a few cortical cysts, about 3 cm. in diameter, on the outer surface. The pelvis and the ureters were normal. The left kidney weighed 350 gm. and was similar to the right. The adrenals appeared slightly atrophic. The bladder and prostate were normal. The brain weighed 1,220 gm. and was essentially normal. The pituitary appeared normal.

Histological examination of the heart revealed the muscle fibers to be normal. In the interstitial spaces between the muscle bundles in focal areas there was an infiltration of polymorphonuclear leucocytes, lymphocyes, and plasma cells. Associated with these inflammatory cells were large irregular mononuclear cells with eccentric nuclei which were somewhat irregular in shape. These resembled cells described in the liver and the spleen. Colonies of bacteria were noted in the heart interstitium. The visceral pericardium was thickened. The aorta was essentially normal. The lungs revealed thickening and hyalinization of the pleura. There was thickening of the alveolar septa, with some atelectasis. There were numerous macrophages within the air sacs. The spleen showed marked congestion of the red pulp and loss of normal splenic architecture. There was marked hyperplasia of the reticuloendothelial histocytic elements. The Malpighian corpuscles could not be made out. There was marked polymorphism of the reticuloendothelial cells. Some were large, with large irregular hyperchromic nuclei; others

had smaller multiple single nuclei, with relatively large amounts of cytoplasm. Evidence of phagocytosis was marked. Hemorrhage was present. In one section there was a large infarct, with complete destruction of the normal tissue architecture. The liver showed marked passive congestion. There was an infiltration of the periportal spaces with lymphocytes and plasma





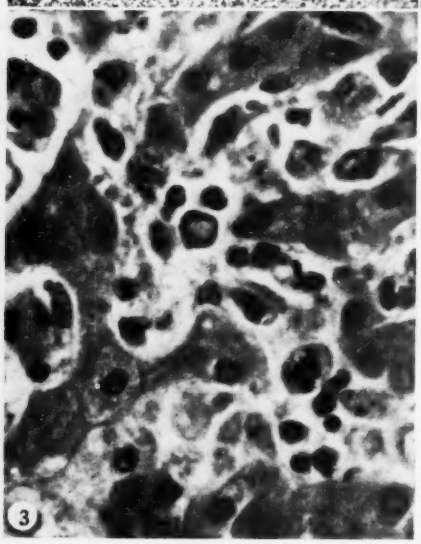


Fig. 1 (Case 1).—Section showing Kupffer cell proliferation and cellular elements in sinusoids of liver; × 100.

Fig. 2 (Case 1).—Section of lymph node showing cellular proliferation and architectural disruption; × 430.

Fig. 3.—Section of a segment approximately in the center of Figure 1; × 430.

cells. The Kupffer cells in the sinusoids showed marked proliferation (Fig. 1) and resembled the reticuloendothelial histocytic elements in the spleen. The adrenals revealed an infiltration into the cortex with reticuloendothelial histocytic cells similar to those described in the liver and spleen. The kidney revealed focal infiltrations of the cortex with reticuloendothelial histocytic cells similar to those described in the spleen. The glomeruli and blood vessels were

markedly congested. There were granular casts within some of the tubules, and in one area there was an old infarction, with hyalinization of the glomeruli and fibrosis of the stroma with destruction of the tubules. The urinary bladder section showed some edema and hemorrhage in the subendothelial layer. The pancreas showed some edema and hemorrhage in the subendothelial layer. The pancreas, stomach, and colon were essentially normal. Histologic sections of several lymph nodes showed destruction of the normal architecture (Fig. 2). Few to no Malpighian corpuscles or germinal centers could be identified. There was marked proliferation of the reticuloendothelial histiocytic cells, with polymorphism (Fig. 3) similar to that described in the spleen. These showed phagocytosis. There was proliferation of histiocytes in the capsular zone, causing a thickening of this zone, as described by McLetchie.[2] The skin sections showed thinning of the epidermis and loss of epithelial pegs. In the subcutaneous tissues, especially surrounding clusters of sweat glands, there were small focal areas of hemorrhage and a slight infiltration of histiocytic cells similar to those described in the internal organs. The bone marrow showed profuse proliferation of reticuloendothelial cells with phagocytic characteristics. Nowhere were cells of the Reed-Sternberg type seen.

The microscopic diagnosis was histiocytic medullary reticulosis or generalized reticuloendotheliosis.

CASE 2.—A 40-year-old Portuguese man was admitted to Queen's Hospital on Jan. 4, 1954, with the chief complaint of swollen nodes on both sides of the neck and the loss of 40 lb. (18 kg.). The patient stated that he first began to lose weight about one month before admission. This was associated with vague abdominal pains and spiking fever, with temperatures that ranged between 98 and 103 F. About two weeks before admission he noted the swelling of nodes on both sides of the neck and moderate shortness of breath.

Physical examination on admission showed a thin cachectic middle-aged Portuguese man in moderate distress. The head, ears, eyes, nose, and throat were not remarkable except for wasting of the tissues. The neck showed enlarged discrete nodes bilaterally in the postauricular, postcervical, and supraclavicular chains. The heart rhythm was regular, and no murmurs were heard. The chest was emphysematous in type, and inspiratory and expiratory moist rales were heard.

There was slight diffuse abdominal tenderness, and the liver was palpable 3 cm. below the right costal margin. The spleen was not palpable. The epitrochlear, axillary, and inguinal nodes were slightly enlarged and discrete but not tender. The extremities showed wasting.

Laboratory studies showed a red blood cell count of 1,800,000, with hemoglobin 6.0 gm. The white blood cell count was 8,400, with differential count of 70% polymorphonuclear leucocytes, 20% lymphocytes, and 5% monocytes; a few neucleated red cells were seen. Urine analysis showed a specific gravity of 1.012; the reaction for albumin was 1+, and for sugar negative. Microscopic examination of sediment showed a few hyaline and finely granular casts. A nonprotein nitrogen determination was 38 mg. per 100 cc. A Coombs test was negative. Anterior-posterior and lateral x-rays of the chest showed a mild generalized emphysema with no definite evidence of mediastinal gland enlargement. A biopsy of the cervical node was reported as showing atypical Hodgkin's disease (or a reticuloendotheliosis). The patient's course in the hospital was downhill in spite of nine transfusions with 500 cc. of whole blood, corticotropin 75 mg. three times a day, iron orally, and multivitamin tablets.

During his stay he ran a spiking fever, with temperature that varied from 98 to 103 F. each day and then returned to normal. His pulse kept pace with the fever, ranging between 90 and 120 beats per minute. A repeated blood cell count after multiple transfusions showed correction of anemia, but there was rapid recurrence. The coagulation time was 5 minutes 30 seconds, and bleeding time was 2 minutes. A platelet count was 19,000 per cubic millimeter. On Jan. 23, 1954, the patient began to develop icterus along with petechiae over the abdomen and chest. Epistaxis, bleeding from the gums, and tarry stools also developed. The patient gradually became weaker and more emaciated and died on Jan. 24, 1954, at 9 a. m.

The essential autopsy findings were that the body was that of an emaciated 40-year-old Portuguese man with multiple petechial hemorrhages over the trunk, arms, and legs. The neck showed multiple small firm movable nodules beneath the skin. Lymph nodes were also palpable in the supraclavicular fossa. The right lung weighed 650 gm. and was gray-tan. The posterior

portion of the lungs was purple. The lungs were crepitant on palpation. The cut surface was tan and showed a moderate amount of frothy fluid. The lung was densely adherent to the chest wall.

The left lung weighed 700 gm. and showed a similar picture. The left pleural cavity contained 500 cc. of bloody fluid.

The peribronchial nodes were enlarged to 2.5 cm. and showed a brownish homogeneous surface on cut section. The superior mediastinum showed multiple enlarged lymph nodes. These nodes were anterior to the large vessels and measured up to 3 cm. in diameter. The areolar tissue surrounding the trachea and esophagus and aorta showed numerous firm small white lymph nodes. The pericardium was clear and smooth and contained 20 cc. of straw-colored fluid. The heart weighed 200 gm. and showed a few white patches on the epicardial surface at the apex. The papillary muscles were normal. The coronary ostia were patent. The tricuspid valve measured 7 cm., the pulmonic valve, 7 cm., and the mitral valve, 8.5 cm. The left ventricle

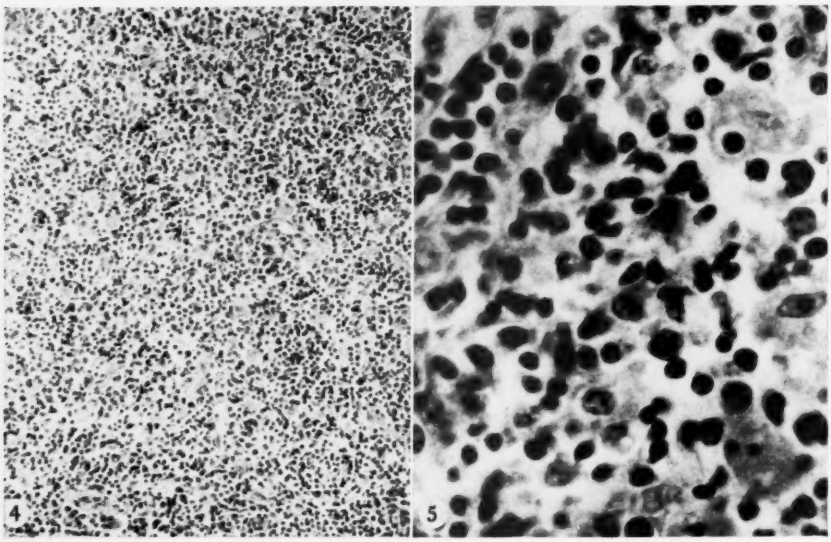


Fig. 4 (Case 2).—Section showing cellular proliferation and architectural disruption of a lymph node; × 100.

Fig. 5.—Section of a segment approximately in the center of Figure 4; × 430.

measured 1.5 cm. and the right, 0.6 cm. in thickness. The gastrointestinal tract was normal. The liver weighed 2,300 gm. and extended 3 cm. below the right costal margin. It was mottled purple, and the surface was smooth. The gall bladder and pancreas were normal. The spleen was enlarged and firm, weighing 1,650 gm. It was densely adherent to the under side of the diaphragm. The capsule was thickened and gray. There was a moderate amount of hemorrhage at the pedicle insertion. The cut surface showed firm tan wedge-shaped areas extending toward the center of the spleen. One third of the plup was replaced by this tissue. The central portion of the organ was soft and purple. The right kidney weighed 230 gm. The capsule stripped with difficulty, leaving a granular surface beneath. On cut section the pyramids were poorly defined. The pelvic fat and ureter seemed normal. The left kidney weighed 110 gm. and presented a similar picture. The adrenals, bladder, prostate, and testicles were normal in appearance. Retroperitoneal lymph nodes in the lumbar region were enlarged and measured 2 to 3 cm. The cut surface was tan. The bone marrow appeared grossly normal.

Microscopic sections of the lymph nodes stained with hematoxylin and eosin revealed marked reticuloendothelial hyperplasia (Fig. 4). There were large fat-filled hystiocytes, histio-

cytes phagocytizing other particles, and nonphagocytic giant cells with pale cytoplasm and multiple hyperchromatic nuclei. Also present were numerous mononucleated and multinucleated phagocytic cells with small pale oval to round nuclei and pale eosinophilic cytoplasm. The nuclei of some of these cells were indented. Plasma cells and lymphocytes were interspersed among these other cells (Fig. 5). There was diffuse involvement, with architectural distortion, but the most marked changes were medullary. Numerous irregular areas of coagulation necrosis were noted.

The spleen showed proliferation of the same cellular elements, with loss of recognizable Malpighian corpuscles, hemorrhage, and necrosis.

The liver presented obliteration of sinusoids by proliferation of Kupfer cells showing marked tendency toward phagocytosis.

Similar cellular proliferations were present in the adrenals and bone marrow.

Again, the microscopic diagnosis was histiocytic medullary reticulosis or generalized reticuloendotheliosis.

COMMENT

The terminology of cells of the reticuloendothelial system is quite variable. Robb-Smith [7] and his group differentiate primitive reticulum cells, prohistiocytes, histiocytes, macrophages, lymphoblasts, lymphocytes, monoblasts, monocytes, and dictyocytes. At the other end of the scale is the simplified classification of reticulum cells and lymphocytes. While the latter classification is almost universally considered as being oversimplified, the former may be too discriminating. In histological study it appears difficult to separate macrophages, histiocytes, reticulum cells, etc. Then, of course, littoral cells of the sinuses and sinusoids must be placed in the same category.

There will be no attempt to go into this argument, but a slight clarification may be helpful. Almost all authorities feel that there are in the body so-called primitive reticulum or mesenchymal cells. From these ultimately stem, among other things, the cells of the reticuloendothelial system or, as used in a narrow sense, the cells of the phagocytic system. Also from these cells stem the hemic cells and the littoral cells lining blood spaces. A fourth line of differentiation appears to be that of fibroblastic cells.

In the cases described here, the proliferation affected especially the cells of the phagocytic type, variously classified as reticulum cells, histiocytes, prohistiocytes, macrophages, and clasmatocytes. The littoral cells in the spleen, liver, and lymph nodes assume phagocytic properties, and these added to the above comprise the "reticuloendothelial system" in the limited sense. There were excessive numbers of plasma cells and lymphocytes also, but these may have been infiltrative.

Not only are the cells of the system a matter of controversy but the terminology of diseases of the system is likewise controversial. On one hand, some authorities feel that proliferations of the reticuloendothelial system (primitive mesenchymal cells) without differentiation or with differentiation along hemic lines are the only true reticuloendothelioses. If these primitive cells form true tumors, reticulum cell sarcomas and lymphosarcomas are formed. These authorities are opposed to the acceptance as an entity of reticuloendotheliosis of a histiocytic nature, considering it merely as a generalized response to an infection such as typhoid, brucellosis, etc.

There is a second school of thought which considers reticuloendotheliosis to include generalized proliferations of histiocytic character wherein the causative agent is unknown.

There is a divergence of opinion among authorities, regardless of which of the above concepts they hold, as to the classification of Hodgkin's disease. Some hold it to be a tumorous type of reticuloendothelial neoplasia, and others consider it to be of infectious (inflammatory) origin.[6]

It should be stated that in the literature the words reticuloendotheliosis and reticulosis are used interchangeably.

The British, under the guidance of Robb-Smith, have classified the conditions affecting the reticuloendothelial system on a purely histological basis.

The reader is referred to Robb-Smith's excellent article [7] for the finer details. In a cursory fashion Robb-Smith divides lymph nodes (and these of course are a major element in the reticuloendothelial system) into follicles, medulla, and sinuses. Then, depending on the cellular proliferation, there are such conditions as histiocytic medullary reticulosis, lymphoid follicular reticulosis, etc. McLetchie [2] has simplified the terminology by failing to recognize a basic difference between the reticulum cell, in a limited sense, and the histiocyte. The diseases presently under discussion are classified as a histiocytic medullary reticulosis according to this simplification. It must be noted that in this and other reported cases the proliferation was not limited to the medullae in lymph nodes. The American classification would vary between an infective reticulosis (reticuloendotheliosis), a nonliquid reticuloendotheliosis, and, in the second case, atypical Hodgkin's disease.

The disease under discussion, in its manifestations clinically and pathologically, is lumped in the category of Hodgkin's disease or is vigorously rejected from it. This of course depends on one's criteria for Hodgkin's disease. Some require tumor formation; others say that Reed-Sternberg cells are not pathognomonic of Hodgkin's disease. The controversy cannot be settled here. However, the absence of any cells resembling those of the classic Reed-Sternberg type and the lack of tumor-like collections in these cases would appear to rule out the possibility of Hodgkin's disease.

Klemperer,† who saw the slides from the first case, in a personal communication to one of us (W. H. C.) said that this case showed a reaction to an infectious process and should not be placed in a special category histologically. With this the authors cannot argue.

Nevertheless, from a clinical standpoint the pictures are quite characteristic, and the diffuse histiocytic proliferations at least justify consideration of these cases as falling into a clinicopathologic syndrome. Scott and Robb-Smith [1] have recognized such an entity since 1939. The entity has been related to the Letterer-Siwe syndrome described in children. It has been placed midway between purely infectious processes of proved etiology causing histiocytic proliferation (typhoid, brucellosis, etc.) and "infectious-neoplastic" processes such as Hodgkin's disease.

The purpose of this paper is to call attention to a repetitive clinical phenomenon associated with a peculiar pathologic picture. Whether infection or some other stimulative process causes this has as yet not been determined. In time, perhaps multiple etiologies will be discovered. At present we can only wait and see. The clinical picture referred to includes a relatively rapid course (one to six months), high irregular fever, wasting, splenomegaly, hepatomegaly, moderate lymph node enlargement, anemia, leucopenia, thrombocytopenia, hemorrhagic manifestations,

† Klemperer, P.: Personal communication to the author.

jaundice, and, often, necrotizing lesions. This is certainly not the usual course of a common infection or of Hodgkin's disease. The resemblance of the course of this disease in adults to that of classic Letterer-Siwe syndrome in children is striking.

SUMMARY

Two cases showing the clinical and pathological findings of histiocytic medullary reticulosis (generalized reticuloendothelosis) have been described. The clinical picture is that of fever, wasting, splenomegaly, hepatomegaly, lymphadenopathy, anemia, hemorrhage, jaundice, and necrotizing lesions. The pathological picture is that of more or less generalized proliferation of histiocytes with phagocytic properties, especially in the liver, spleen, lymph nodes, and bone marrow.

Mr. Larry Wells provided the photomicrographs.

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TREATMENT OF ACUTE LEUKEMIA WITH CORTISONE AND CORTICOTROPIN

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ALTHOUGH the usefulness of the hormones corticotropin and cortisone in the treatment of acute leukemia has become quite clear, little consideration has been given to the possible reasons for the effectiveness of these agents in some cases and their failure in others. We have become impressed that in certain cases the course of the illness has even seemed to become accelerated in association with such hormone therapy. A review of our own experience was therefore initiated and the present report represents the results of that study.

REVIEW OF LITERATURE

A review of the literature reveals that others have made somewhat similar observations, although a critical analysis of experience in a single clinic has not been published. In Table 1 a summary is given of the recorded data. Unfortunately, a number of investigators have not attempted to differentiate the various types of acute leukemia. Others have done so, but criteria for their classification are not given. To add to the confusion is the fact that it has not always been made clear just what is regarded as a very good response or a less impressive one. Finally, the doses used have varied greatly.

Pearson and Eliel [1] observed good clinical and hematological remissions in 13 out of 27 patients with acute granulocytic and lymphocytic leukemia and noted no difference in response in the two groups. Acute monocytic leukemia did not seem to be affected by hormone therapy. The reported improvement on corticotropin (ACTH) therapy in a case of monocytic leukemia described by Kinsell and associates [3] is difficult to evaluate because the condition of the patient became worse at first and improvement took place only later, following an acute infection and after the dose was reduced. Videbaek [4] produced little benefit with corticotropin therapy in his case of acute monocytic leukemia, and Taylor and associates [5] noted a progres-

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sively failing course in their two cases of acute and subacute myelogenous leukemia. Reisner [6] did not consider that lymphoblastic leukemia is the most susceptible of the acute leukemias but acknowledged that, of three cases of monocytic leukemia, two became worse and one showed no response.

Schulman and associates [7] did not attempt to classify cases of acute leukemia in which no evidence of differentiation beyond the "blast" stage was present but grouped such cases simply as "acute leukemias." Of nine cases belonging to this group, six showed complete and two showed partial remission. They noted, however, that a 6-year-old boy with acute granulocytic (monocytoid) leukemia failed to respond to large doses of cortisone and died one week after an 18-day course of the hormone. A 3½-year-old boy with a six weeks' history of illness, who was regarded as having subacute myeloid leukemia, received corticotropin for 21 days. There was no clinical improvement, and the leucocyte count increased from 129,000 to 225,000 per cubic millimeter. An excellent clinical and hematologic remission followed institution of amethopterin (4-amino-N^{10}-pteroylglutamic acid) therapy.

In the report of Rosenthal and associates,[9] of five patients with acute granulocytic leukemia only one showed slight clinical improvement with therapy. In two cases, as well as in two cases of monocytic leukemia, the leukemic process seemed to be accelerated. On the other hand, definite hematological and clinical remission was observed in 9 of 13 cases of the lymphocytic form. No convincing improvement was induced in nine patients of all ages described by Cameron and co-workers.[10] Seven of these patients were considered to have acute granulocytic leukemia; one had acute lymphocytic leukemia, and one was classified as having "stem cell" leukemia. Darte and associates [11] did not indicate the type of acute leukemia in most of their 37 cases, but, of 3 cases classified as acute granulocytic leukemia, a remission was observed in 1, no effect was seen in the second, and there was apparent aggravation in the third. Of the remaining 31 unclassified cases, "complete" remissions were oberved in 17.

Farber [12] and Pierce [13] did not differentiate their cases of acute leukemia. All their patients were children. Bethel [14] observed deterioration rather than improvement in his seven cases of acute leukemia in adults, of which two were lymphocytic; three granulocytic, and two monocytic. The best results in the series of Adams and associates [15] were observed in a case of lymphoblastic leukemia and in an unclassified case; however, a good remission occurred in one case judged to be myeloblastic.

Bernard and Bessis [16] did not differentiate their acute leukemias. The results of steroid hormone therapy in Great Britain, as reported by a panel of the Medical Research Council,[17] were not very encouraging in any type of acute leukemia, perhaps because of insufficient dosage; nor was a second report [25] much more encouraging. The same is true of the reports of Davidson and associates,[19] Suzman,[22] and Wilkinson.[24] Of the 20 children with acute or subacute lymphatic leukemia reported by Stickney and associates,[20] complete remissions were observed in 5, partial in 2, and none in 13. They stated that cortisone and corticotropin were occasionally effective in leukemias of other varieties.

Gasser and Cramer [21] distinguished between "paraleucoblastic" leukemia and leukemia with good evidence of differentiation. Of 11 cases of the former, good remissions were observed in 8; partial remissions, in 3. On the other hand, one patient with "promyelocytic" leukemia showed very slight improvement and

another showed marked aggravation. A third, with well-defferentiated myeloid leukemia and no "hiatus leukaemicus," also became worse on therapy, and the leukocyte count rose from 158,000, to 650,000 cells per cubic millimeter. In a case of systemic reticuloendotheliosis suggestive of acute monocytic leukemia of the Schilling variety, in a child, Gray [23] observed a rapid rise in the leucocyte count and death occurred within seven days. The patient of Aber and associates [26] with subacute myeloid leukemia, on the other hand, seemed to improve with corticotropin therapy, in spite of an increase in the leucocyte count during the first two weeks of treatment.

TABLE 1.—*Reported Results of Steroid Hormone Therapy in 425 Cases of Acute Leukemia*

	Lymphoblastic Leukemia				Myeloblastic Leukemia				Monocytic Leukemia				"Acute" (Undifferentiated) Leukemia			
	Total Cases,	Remissions*			Total Cases,	Remissions			Total Cases,	Remissions			Total Cases,	Remissions		
	No.	C	P	F	No.	C	P	F	No.	C	P	F	No.	C	P	F
Pearson & Eliel [1]	..	..	..	..	..	..	..	..	3	..	..	3	27	13	9	5
Spies & others [2]	..	..	..	..	1	..	1	..	..	..	..	..	4	1	2	1
Kinsell & others [3]	..	..	..	..	..	..	..	..	1	1	..	..	..	..	..	..
Videback [4]	..	..	..	..	..	..	..	..	1	..	1	..	1	..	..	1
Taylor & others [5]	..	..	..	..	2	..	..	2	..	..	..	..	..	..	..	..
Reisner [6]	..	..	..	..	..	..	..	..	3	..	..	3	..	..	..	..
Schulman & others [7]	..	..	..	..	1	..	..	1	1	..	..	1	9	6	2	1
Rosenberg & others [8]	11	7		4	1	..	..	1	2	..	..	2	1	..	..	1
Rosenthal & others [9]	13	8		5	5	..	1	4	2	..	..	2	..	..	..	..
Cameron & others [10]	1	..	..	1	7	..	1	6	..	..	..	..	1	..	..	1
Darte & others [11]	..	..	..	..	3	1	..	2	..	..	..	..	33	17	4	12
Farber & others [12]	..	..	..	..	..	..	..	..	..	..	..	..	37	9	16	12
Pierce [13]	..	..	..	..	..	..	..	..	..	..	..	..	20	14		6
Bethell [14]	2	..	..	2	3	..	..	3	2	..	..	2	..	..	..	..
Adams & others [15]	2	..	1	1	3	1	..	2	..	..	..	..	1	1	..	..
Bernard & Bessis [16]	..	..	..	..	..	..	..	..	..	..	..	..	66	19	32	15
Medical Research Council, 1st Rep. [17]	12	..	5	7	16	1	3	12	5	..	..	5	3	..	..	3
Bierman & others [18]	15	7		8	..	..	..	..	..	..	..	..	..	..	..	..
Davidsohn & others [19]	1	..	..	1	1	..	..	1	..	..	..	..	..	..	..	..
Stickney & Mills [20]	20	5	2	13	..	..	..	..	..	..	..	..	..	..	..	..
Gasser & Cramer [21]	..	..	..	..	3	..	1	2	..	..	..	..	11	8	3	..
Suzman [22]	4	..	2	2	2	..	..	2	..	..	..	..	..	..	..	..
Gray & Taylor [23]	..	..	..	..	..	..	..	..	1	..	..	1	..	..	..	..
Wilkinson [24]	20	2	8	10	19	1	5	13	5	..	..	5	..	..	..	..
Medical Research Council, 2nd Rep. [25]	9	1	1	7	4	..	..	4	..	..	..	..	3	..	..	3
Aber & others [26]	..	..	..	..	1	..	1	..	..	..	..	..	..	..	..	..
Total, 425	110	30	19	61	72	4	13	55	26	1	1	24	217	88	68	61

* C, complete; P, partial; F, failure.

In Table 1 the reported results in 425 cases of acute leukemia are listed. From the viewpoint of critical analysis, the data are subject to the defects already mentioned. Nevertheless, it is rather impressive that "complete" remissions have been so rare in cases classified as myeloblastic (5.5%) or monocytic (3.9%), whereas the figure for the lymphoblastic cases is 27.3%. Among the cases classified only as "acute," complete remissions were observed in 42.5%.

Since it is well recognized that the response to therapy is usually better in children than in adults, it would be helpful if the published data could be classified according to age, unfortunately, this is not possible in many instances. In the reports

which have been reviewed it has been possible to discover clear statements concerning age, type of leukemia, and response only for 173 children. Many of the remaining 252 reported cases were children, but the information given is not explicit. Of the 173 cases in children, the incidence of "remissions" was 70% in 113 cases of "acute" leukemia, 50% in 49 cases classified as lymphoblastic leukemia, and 25% in 8 cases of myeloblastic leukemia, with no remissions in 3 cases of monocytic leukemia.

METHOD OF STUDY

All of our cases of acute leukemia receiving cortisone or corticotropin therapy have been reviewed. Only those which received the medication for less than one week and those whose course could not be followed at frequent intervals have been excluded.

Differentiation of the various types of acute leukemia was made on the basis of criteria described elsewhere.[27] In order to make this as objective as possible, blood and bone marrow smears from each of the cases were reviewed by one of us (M.M.W.) without knowledge of their source. The survey of all the blood and bone marrow smears was made at one time. Only material obtained prior to the beginning of therapy was used. When there were few or no abnormal cells in the blood, bone marrow smears were examined. This was also done in many instances when blood smear examination alone might have been adequate.

The differentiation of the several types of acute leukemia is admittedly difficult. In attempting this, details of the nuclear structure were considered to be of great importance. In preparations stained with Wright's stain the term "myeloblast" was applied to cells with a smooth nuclear membrane, even in outline and exceedingly thin, with no condensation near the inner surface. In cells classified as "lymphoblasts" the nuclear membrane was more dense. The chromatin of the myeloblasts appeared to be made up of very fine strands or fine dust-like granules and was evenly and diffusely distributed, with no aggregation into larger masses, except for occasional condensation about the nucleoli. The chromatin of the lymphoblasts was coarser and showed some aggregation. In the myeloblasts there often were two to five nucleoli, pale sky blue, whereas only one or two nucleoli were usually present in the lymphoblasts. Monoblasts were not distinguished from myeloblasts. The recognition of monoblastic leukemia depended on the presence of significant numbers of cells with the characteristics of monocytes.

The peroxidase stain of Sato and Sekiya proved useful in bringing out cytoplasmic granulation when this was not clearly demonstrable by Wright's stain. The findings of an occasional immature granulocyte, however, was not considered alone as proof of differentiation towards the granulocytic series; such cells are seen in "myelophthisic" states other than leukemia, and their presence can be likened to the presence of normoblasts in the blood in leukemia. Naturally, no difficulty was encountered in the cases presenting good evidence of differentiation toward more mature forms in the granulocytic series or in the cases of monocytic leukemia. Difficulty arose in cases in which nongranulated and peroxidase-negative cells dominated the picture. Some hold that differentiation in such cases is impossible. We freely admit the possibility of error, and it is for this reason that the classification of the cases was made as objectively as possible.

Response to therapy was classified under three headings; namely, complete remission, partial remission, and failure.

Group I, "Complete Remission".—These cases met the following criteria:

Regression of enlarged organs to normal limits

Disappearance of bone tenderness

Disappearance of bleeding manifestations

Gain in weight not attributable to retention of fluid

Return of hemoglobin or volume of packed red cells, platelets, and leucocyte count to normal levels

Normalization of the differential leukocytic count: disappearance of abnormal cells as well as increase of mature granulocytes to essentially normal numbers

Levels of hemoglobin above 12 gm. per 100 ml. (or a volume of packed red cells above 40 ml. per 100 ml.) were considered to be normal for the present study. For platelets, figures close to or above 200,000 per cubic millimeter were considered adequate. As regards the leucocytes, chief importance was given to the presence of an adequate number of mature granulocytes (3,000 per cubic millimeter or more) and the absence of "blasts." The presence of an occasional cell (1 to 2%) which could or could not be definitely classified as a "blast," while the remaining cells were normal in appearance, was not considered as excluding a complete remission. However, an increase of such cells percentage-wise or in absolute numbers was taken as evidence of relapse.

Reversal of bone marrow findings to normal was not included as a criterion, since bone marrow examination was not done routinely in all cases, especially in children and infants. Although it is admitted that bone marrow examination will provide more information concerning the status of the disease process than the clinical and blood findings, it was thought that a normal blood picture reflected adequate bone marrow activity even though the bone marrow might not be entirely normal. Bone marrow examinations were made, however, in all cases in which the clinical and blood findings left some doubt as to the completeness of the remission. The term "complete" is recognized, of course, as being imperfect as a designation of the result achieved, since, invariably in acute leukemia, relapse ultimately occurs.

The duration of the remission was not included as a criterion of its completeness.

Group II, "Partial Remission".—In these cases only moderate clinical and/or hematological improvement took place. Although some of the symptoms and signs were modified considerably, the blood values failed to return to normal levels, as defined above, in spite of a marked decrease in the number of "blasts" in the blood. In other cases the improvement in the hematological picture was greater than the degree of regression of the enlarged organs. In all cases the extent and degree of improvement was not as great as in Group I.

Group III, "Failure."—In these cases neither clinical nor hematological improvement occurred and the disease progressed, apparently uninfluenced by therapy.

Subjective improvement alone, so common at the beginning of hormone therapy, has not been included as a criterion of improvement. Increase in appetite and energy was often seen in the absence of objective improvement and, therefore, was also excluded from the criteria.

The cases have been separated into three groups according to age because of the difference in the response at different ages. These groups are (1) children 10 years and younger, (2) patients 11 to 20 years of age, and (3) patients over 20 years of age.

RESULTS (TABLE 2)

1. CHILDREN TEN YEARS AND YOUNGER (27 CASES)

(*a*) *Acute Lymphoblastic Leukemia* (22 Cases).—Of the 22 children with this type of leukemia, a complete remission was observed in 18; partial remission occurred in 3, and no remission occurred in 1.

The clinical changes associated with successful hormone therapy have been described by many investigators and need not be repeated in any detail. Cortisone was used as a rule, in doses of 50 to 200 mg. (usually 100 to 150 mg.), in preference

TABLE 2.—*Comparison of Effectiveness of Cortisone or Corticotropin in Treatment of Various Types of Acute Leukemia at Different Ages*

Age Group, Yr.	No. of Cases and Type of Leukemia	Remission		Failure
		Complete	Partial	
10 or younger	22 lymphoblastic	18	3	1
	4 myeloblastic	0	2	2
	1 monoblastic	0	0	1
11-20	4 lymphoblastic	1	2	1
	3 myeloblastic	0	0	3
Adults	5 lymphoblastic	2	2	1
	8 myeloblastic	0	0	8
Totals	31 lymphoblastic	21	7	3
	15 myeloblastic	0	2	13
	1 monoblastic	0	0	1

to corticotropin, because of the ease of oral administration. The daily dose was divided in three or four equal amounts and was given at eight- or six-hour intervals, respectively. At the same time, potassium chloride was prescribed, in doses of 2 to 5 mg. daily, as well as a diet low in salt. Corticotropin was used exclusively in only one case, and it was used together with cortisone in another two cases for a short period.

Beneficial effects usually appeared promptly, fever, if present, disappearing, appetite improving, and hemorrhagic manifestations clearing, the last before any increase in the platelet count was detected. Improvement was often clearly evident within a week, sometimes even in several days, occasionally not for two weeks. Signs of hypercorticism developed in all of the patients; these appeared usually after 7 to 12 days of therapy and became accentuated progressively.

The duration of cortisone treatment ranged from 19 to 55 days, with the exception of a case that is considered a failure, in which cortisone was given for 12 days only, at which time the patient died. Most patients received the therapeutic dose of cortisone for four to five weeks, with an additional week or 10 days for gradual cessation of therapy. The total dosage for the first course of therapy ranged from 750 to 5,650 mg., equivalent to 152 to 390 mg. per kilogram body weight. In most cases this amounted to 5 to 10 mg. per kilogram per day.

Hematological Response: The time within which the hematological changes took place ranged within fairly narrow limits in those responding favorably. Likewise, the changes in the blood followed a surprisingly constant pattern.

Total number of leucocytes. When the number of leucocytes was increased at the institution of therapy, a dramatic decrease sometimes would take place within the first few days. By the end of the first week leucopenic levels were reached in most cases (Fig. 1). There was only one exception among the 15 closely followed cases. In this case the initial count was unusually high (400,000 per cubic millimeter).

When there was initial leucopenia, this became more accentuated during the first week of therapy. Only one exception to this was observed. In no case was there an increase in the leucocyte count in the first week; an increase during the second week was observed only in one case.

During the second week the reduced or definitely leucopenic levels were usually maintained, or a slight rise sometimes occurred. In a few instances the leucocyte count became still lower.

From this time on, during the third and fourth weeks, the leucocyte count rose, and normal levels were usually reached by the end of the fourth week. In some instances leucocytosis developed at this stage, as the result of an increase in polymorphonuclear leucocytes.

Differential count. The changes in the total leucocyte count corresponded to definite changes in the differential count. The fall in the count was due to the disappearance of the circulating "blasts" and possibly to a reduction of lymphocytes as well. The subsequent rise was accounted for by the reappearance of normal granulocytes (Fig. 2). In some instances the "blasts" disappeared completely before the normal cells started to increase.

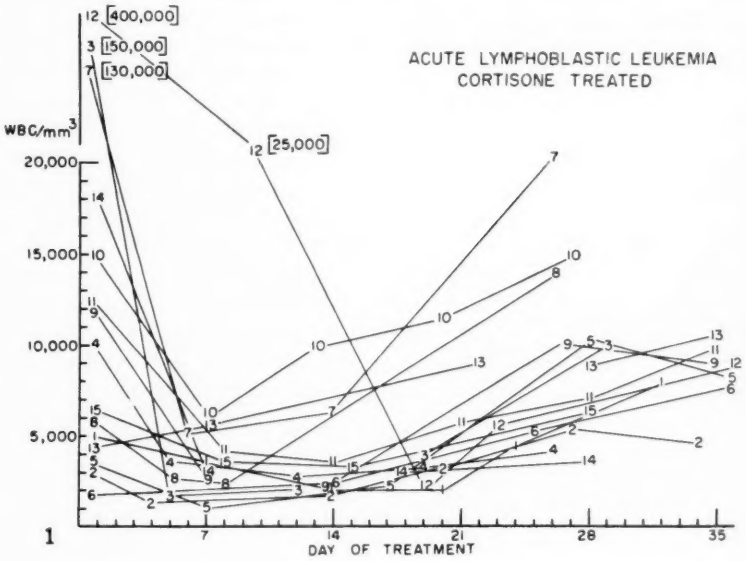
Hemoglobin (Fig. 3). During the first week of therapy a decrease was observed. This occurred in the patients who had been given transfusions and brought to artificially higher hemoglobin levels. Those who had not been given transfusions and those in whom the initial hemoglobin level was rather low did not show this tendency.

By the end of the second week of therapy an increase in hemoglobin was already manifest, and from then on the increase continued throughout the third and fourth weeks. At the end of this time normal or slightly subnormal levels were reached. Following this, the hemoglobin sometimes continued to rise and attained values rather high for this age group.

Reticulocytes. Reticulocyte counts were not done routinely in these cases.

Platelets (Fig. 4). In most cases a rapid increase in platelets occurred during the second week, and this continued during the third and fourth weeks or leveled off if normal levels were reached earlier. In all the cases normal, higher than normal, or, in any event, entirely satisfactory levels were reached by the end of the fourth week.

In summary, the pattern of hematological response was rather constant in the cases responding well to cortisone therapy. In most cases, evidence of a favorable response could be seen during the first week of therapy. Satisfactory blood values were attained by the end of the fourth week, at most during the fifth, if no complications were present.



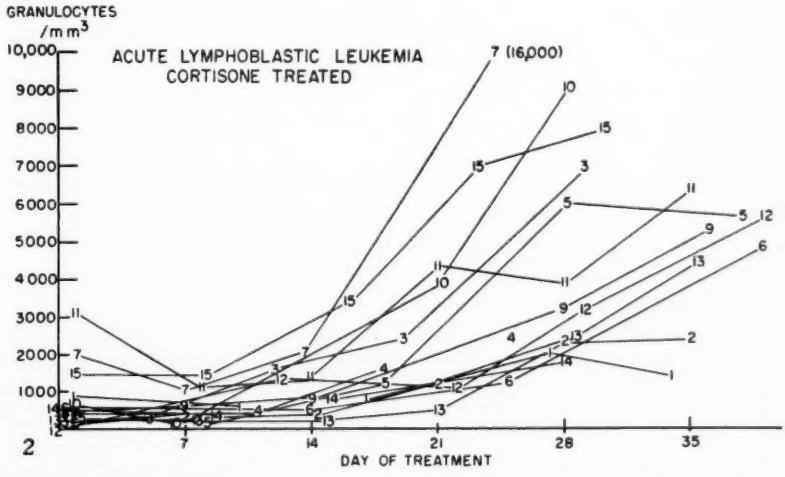
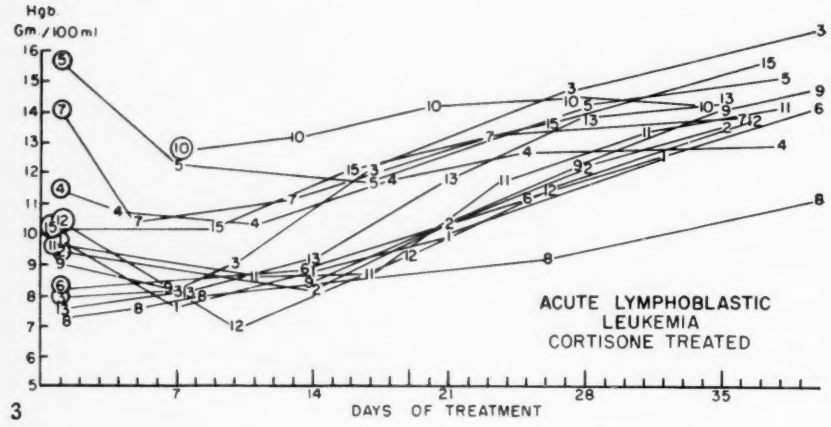


Fig. 1.—Total leucocyte counts in 15 cases of acute lymphoblastic leukemia responding to cortisone or corticotropin therapy. Only the frequently examined cases are included. Numbers correspond to individual cases.

Fig. 2.—Granulocytes in 14 cases of acute lymphoblastic leukemia responding to cortisone or corticotropin therapy. Numbers correspond to the same cases as in Figure 1.

The speed or ease with which the remission occurred did not seem to be related to the duration of the remission. In some cases which remitted promptly and easily relapse took place shortly after the optimal blood values had been attained. The duration of the remission, as measured from the time it was considered to be com-



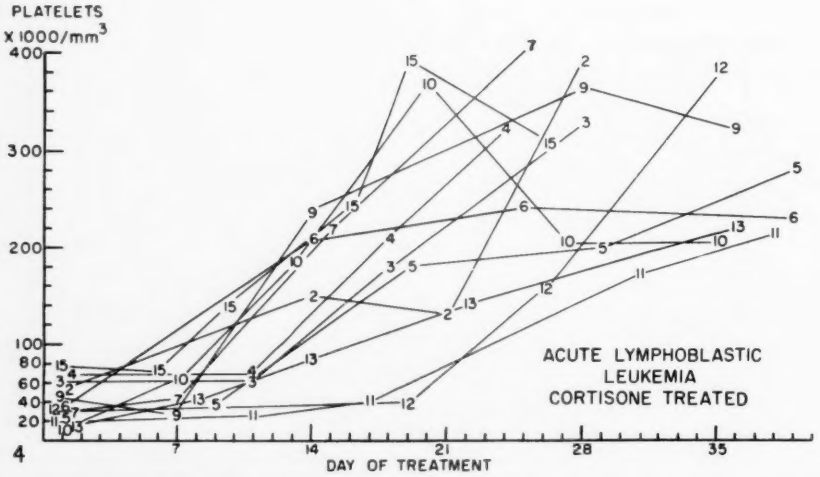


Fig. 3.—Hemoglobin levels in 14 cases of acute lymphoblastic leukemia responding to cortisone or corticotropin therapy. Case numbers are the same as in Figure 1. Those in circles refer to patients who were given transfusions either immediately before therapy or earlier in the course of their disease, with the exception of Case 10. This patient had a transfusion during therapy. The remaining cases did not have transfusions.

Fig. 4.—Platelet counts during cortisone therapy in 12 cases of acute lymphoblastic leukemia. Case numbers are the same as in Figure 1.

plete until the appearance of the first convincing signs of clinical and/or hematological relapse, varied considerably, from one week to three months. Of the 11 cases in which the time could be ascertained accurately, 6 relapsed within 40 days. In all

these cases but one cortisone administration was stopped when a complete remission had been attained, and no other therapy was given. In one patient (Case 1) small amounts of cortisone were continued, but relapse was obvious after two months, nevertheless. In the remaining seven cases, in the hope that the cortisone-induced remission might be prolonged, amethopterin therapy was instituted immediately upon withdrawal of cortisone. In this small group of unselected cases the mean duration of the cortisone-induced remission was 125 days.

Only partial remissions were observed in 3 of the 22 children 10 years of age and under with acute lymphoblastic leukemia. In one of these, a 3-month-old boy, treatment was discontinued after 18 days of therapy, by which time the hemoglobin and platelets were approaching normal although the leucocyte count was still only 1,500 per cubic millimeter, the level to which it had decreased from the initial 65,000 per cubic millimeter. A normal picture was never attained, however, and two weeks after therapy was discontinued the leucocyte count was 52,000 per cubic millimeter, even though the hemoglobin was still increasing.

In the second patient, a boy of 8 months, the clinical and hematological response during the first three weeks was similar to that of cases in Group I. However, in the fourth week, before normal values had been attained, rapid relapse occurred in spite of cortisone therapy. The disease in the third patient, a 5-year-old boy, relapsed similarly during the fourth week of therapy, before normal values were attained, even though the initial response was very satisfactory and similar to that of cases in Group I.

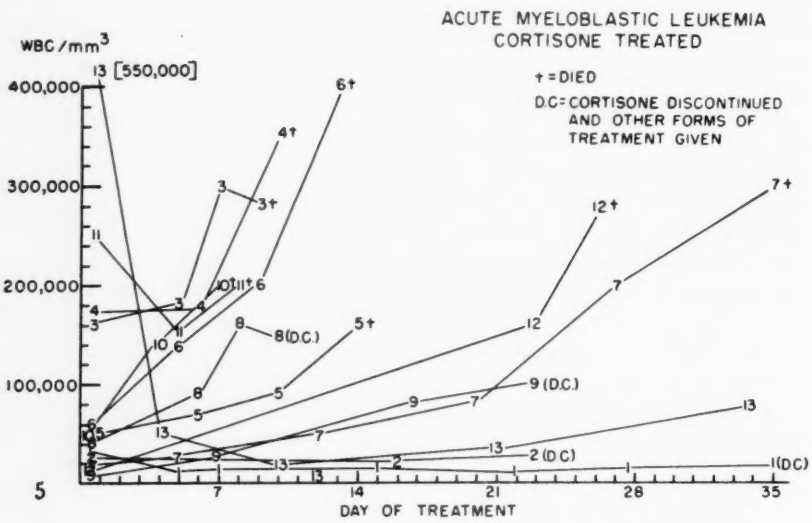
The only complete failure in this group of cases was a patient who died on the 12th day of therapy as the result of pulmonary edema while receiving a transfusion because of severe intra-abdominal and gastrointestinal hemorrhage. In this case, as in the others, a striking drop in the leucocyte count with a reduction in the number of circulating "blasts" occurred after four days of therapy and there was no further increase.

(*b*) *Acute Myeloblastic Leukemia* (4 Cases).—A partial remission was observed in one case after 50 days of therapy on doses of cortisone as high as 150 mg. per day. This, it will be noted, was an exceptionally long period of time and the highest dose of cortisone (450 mg. per kilogram total dose) given in the whole series (Case 1, Figs. 5 and 6). In another case, that of a child of 6 months, clinical and hematological improvement was followed in the third week of cortisone therapy by relapse (Case 13, Figs. 5 and 6). The remaining two children of this age group with acute myeloblastic leukemia failed to show either hematological or clinical improvement, and the disease progressed, apparently uninfluenced by cortisone (one of these is Case 2, Figs. 5 and 6).

(*c*) *Acute Monocytic Leukemia* (1 case).—The single patient in this age group died on the 12th day of therapy. It seemed as if there had been rapid aggravation of the leukemic process (Case 3, Figs. 5 and 6).

2. Patients Eleven to Twenty Years of Age (7 Cases)

(*a*) *Acute Lymphoblastic Leukemia* (4 Cases).—Complete remission was observed in one case, in which there was a complicating severe staphylococcal septicemia. In two cases partial remissions were observed, but cortisone was given



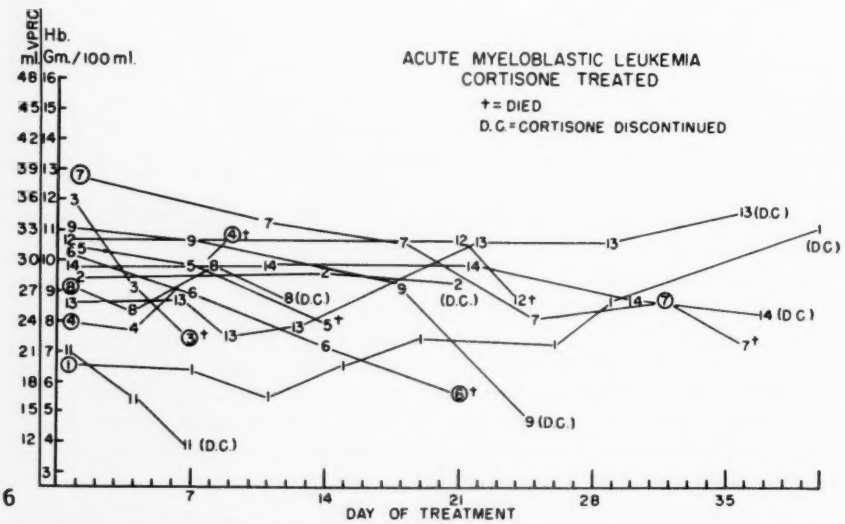


Fig. 5.—Total leucocyte counts in 12 cases of acute myeloblastic or monoblastic leukemia during cortisone or corticotropin therapy.

Fig. 6.—Hemoglobin or volume of packed red cells (VPRC) in 13 patients with acute myeloblastic leukemia under treatment with cortisone or corticotropin. Numbers correspond to the same cases as in Figure 5. Circles about the numbers indicate that transfusion preceded the encircled hemoglobin or VPRC determination.

only in small doses (25 mg.) for 10 days in one case, and no accurate information concerning dosage was available in the other case. Both patients had received the medication prior to their examination by us. It is possible that more adequate therapy would have brought about a more successful result. In an 11-year-old girl 30 days of corticotropin therapy proved entirely ineffective.

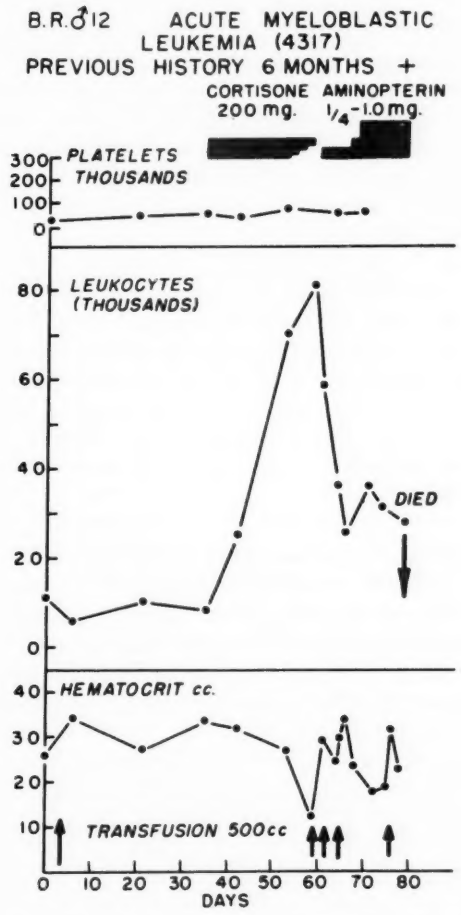


Fig. 7.—Rise in leucocyte count and development of severe anemia in a case of acute myeloblastic leukemia (B. R.) during cortisone therapy. This was accompanied by marked deterioration in the clinical course, which aminopterin therapy failed to interrupt, although a sharp decrease in the leucocyte count was produced.

(*b*) *Acute Myeloblastic Leukemia* (3 Cases).—No benefit whatsoever was observed in three patients with acute myeloblastic leukemia, who received treatment for more than a week. In two, aggravation of the hematological and clinical picture occurred immediately following institution of therapy (Cases 4 and 9, Figs. 5 and 6).

The course of one of these patients is shown in Figure 7. In the third, no evidence of any beneficial effect was evident after eight days of adequate corticotropin dosage (Case 11, Figs. 5 and 6).

3. Patients Over Twenty Years of Age (13 Cases)

(*a*) *Acute Lymphoblastic Leukemia* (5 Cases).—Of the five cases, a complete remission was observed in two. The improvement was comparable to that obtained in acute lymphoblastic leukemia in young children, both in degree and promptness. In one case the remission was maintained on cortisone therapy for one month and maintained for another two and one-half months on subsequent aminopterin therapy. In the second case, with continuous corticotropin administration, remission continued for three weeks, but relapse followed promptly upon withdrawal of corticotropin.

In two cases there were few signs of clinical improvement but evidence of partial hematological remission was supported by bone marrow aspirations. The remaining patient failed to show any convincing signs of improvement.

(*b*) *Acute Myeloblastic Leukemia* (8 Cases).—Of the eight cases, none showed the least evidence of favorable response. In five of these cases it seemed as if the leukemic process was exacerbated. Thus, there was a rapid rise in the total leucocyte count (Fig. 5), an increase in immature forms, increase of anemia (Fig. 6) and bleeding manifestations, enlargement of organs, and general deterioration (Cases 5, 6, 7, 8, and 12, Figs. 5 and 6). In the remaining three cases there was no convincing evidence of aggravation; however, the absence of any improvement was evident enough, and the disease ran its course, apparently without modification by therapy.

SECOND AND FURTHER COURSES OF THERAPY

Twelve of the 27 patients 10 years of age and under were treated a second time with cortisone when relapse occurred following complete remission. Ten of these were examined frequently enough for adequate evaluation. In seven the daily dose was the same as was given during the first course. A higher dose was given in one, and a smaller amount (30 to 50%), in the remaining two. The duration of therapy was 2 to 10 weeks, with one exception (10 days of therapy). The time interval between cessation of the first course and retreatment ranged from seven days to seven months. In all instances the leukemia was lymphoblastic.

Ten cases were observed closely. Three failed to show any evidence of clinical or hematological improvement whatever, although in each a complete remission had followed the first course of treatment. In four, partial hematological improvement, consisting mainly of reduction in the number of circulating lymphoblasts, was seen; in only one of these was there satisfactory clinical improvement. With one exception, the first remissions in these four cases had been complete. In two cases the effect of cortisone cannot be evaluated adequately, as the hormone was given soon after amethopterin was stopped. It is likely that, at least in one of these two cases, the improvement was due to recovery from toxicity produced by amethopterin. Be this as it may, in three weeks both patients were again in obvious relapse. Since excellent responses had been observed in both cases during their first course of therapy, the second courses may safely be considered failures. In the last case of this group there was some symptomatic improvement after a 10-day course of cortisone therapy.

Whatever improvement did occur in these cases was seen after giving cortisone for only 10 to 14 days. Equally poor results were observed when cortisone therapy was reinstituted after short or long intervals (300 days) following the first course of treatment. Furthermore, even when some improvement occurred, it was extremely transient, lasting for only a week or 10 days. A long period of successful antifolic acid therapy did not seem to make the patient any more susceptible to the readministration of cortisone.

Five patients received third courses of cortisone therapy, but only three were followed closely. Two were complete failures, while the third displayed some decrease in the size of the enlarged organs but there was no hematological improvement.

One patient received hydrocortisone (Compound F) in the third course of hormone therapy, at a very advanced stage of the disease. There was a sharp drop in the number of circulating lymphoblasts and a decrease in the size of the enlarged organs, but there was no other improvement, and death followed severe complicating pneumonia.

Of the remainder of the patients with acute lymphoblastic leukemia, two in the group 11 to 20 years of age were given a second course of cortisone. In neither was there any benefit following treatment for three and six weeks, respectively.

Only two adults with acute lymphoblastic leukemia who had shown an excellent response to the first course of steroid hormone therapy received second courses. There was no improvement in one and moderate hematological improvement in the other.

CORTISONE OR CORTICOTROPIN GIVEN FOR THE FIRST TIME AFTER PREVIOUS SPECIFIC THERAPY

With two exceptions, none of the patients discussed until now had received any therapy prior to cortisone or corticotropin other than transfusions and antibiotics. Of the exceptions, one adult, with acute lymphoblastic leukemia, had been given methyl-bis(β-chloroethyl) amine hydrochloride (nitrogen mustard), with no beneficial effects, and the other, an adult with acute myeloblastic leukemia, had been receiving aminopterin when cortisone was started. There was no remission in either patient, and these cases will not be considered further.

Corticotropin or cortisone was given to four children, all under 10 years of age, after therapy with one of the antifolic acid agents. In three of them the remissions could be attributed to these agents, but in the fourth the improvement seemed to be spontaneous and was associated with an acute infection. The total duration of the disease at the beginning of hormone therapy was 5 to 7 months in three cases and 17 months in one.

In three patients excellent clinical and hematological improvement took place, which lasted three weeks, four weeks, and two months, respectively. In the last case aminopterin therapy was continued; however, in spite of the improvement, the marrow showed 60% "blasts" at the height of the remission. In the fourth case a partial remission was associated with corticotropin therapy and the child survived for another 70 days despite complicating mumps and pneumonia.

COMPLICATIONS

Signs of hypercorticism developed to some degree in all but one patient and were evident as early as 7 to 12 days after initiation of therapy. These developed whether or not a remission was achieved. There was no correlation between the successfulness of therapy and the severity of the signs of hypercorticism. The most common signs were "moon facies," abdominal distention, excessive hair growth, and the "buffalo hump." It is of interest that clinical signs of hypercorticism were not seen in an 11-year-old girl with acute lymphoblastic leukemia treated for one month with corticotropin. Histologic examination revealed mild infiltration of the adrenal cortex by leukemic tissue; there was depletion of cortical lipid in the zona glomerulosa, and no medullary tissue was present. This patient had never received cortisone.

Severe generalized osteoporosis occurred in two children and led to collapse of several vertebrae in one. In both cases leukemia had been present for approximately one year when osteoporosis was detected. Convulsions, with increased intracranial pressure, and hallucinations occurred during cortisone therapy in a young boy. These were controlled with diphenylhydantoin (Dilantin) while cortisone therapy was continued. In one patient muscular weakness of the lumbar girdle, simulating the childhood type of progressive muscular dystrophy, developed during the second course of cortisone therapy. The muscular weakness subsided slowly but not completely during the subsequent months when cortisone was replaced with 6-mercaptopurine. At autopsy, six months later, primary atrophy of the muscles was found.

Infections were not particularly troublesome in children receiving cortisone, but in adolescents and adults they represented more of a problem.

COMMENT

The difference between the results of therapy in the cases of acute lymphoblastic leukemia and those in the myeoblastic and monocytic cases proved on analysis to be even more striking than our preliminary impressions had led us to believe. It should be emphasized that the classification of the cases was carried out objectively, without knowledge of their outcome. The review of all of our cases on the basis of uniform criteria changed the initial impression concerning the type of cell involved in two cases (P. L. and H. M.) from myeloblastic to lymphoblastic. The first of these had responded well to therapy, but the second was the only complete failure among the children 10 years of age and under. These two cases were included in an earlier report from this clinic [28] and both received corticotropin therapy. In the case in which this treatment had failed, as stated above, some infiltration of the adrenal cortex by leukemic tissue was found at autopsy. Of the 11 cases of acute leukemia reported in 1951,[28] 3 have been excluded from the present series because therapy had been given for less than one week (P. C., S. T., C. R.).

The susceptibility of acute lymphoblastic leukemia to the induction of remission by hormone therapy and the failure of the other forms of acute leukemia to respond in this gratifying way is borne out by a survey of the literature, as pointed out earlier, even though this difference has heretofore not been stressed.

That there should be such a difference in therapeutic effect is not surprising if the lymphopenia induced by hormone administration and the granulocytic stimulation [28] are recalled.

Remissions were observed at all ages in cases of acute lymphoblastic leukemia, although, as is the case with other forms of therapy in acute leukemia, the remissions were more frequent and more complete in the children 10 years of age and under. They generally were longer in duration in cases in which the initial leucocyte counts were normal or low than in those in which there was marked leucocytosis, although this was not true invariably. Relapses during therapy, before the progressing remission had become complete, occurred exclusively in cases marked by high leucocyte counts. No clear relationship could be made out between the length of time patients had been under treatment with hormone and the readiness with which a relapse set in following remission. Nevertheless, it is our impression that it may be wise to prolong cortisone therapy for a week or two beyond the time when the remission seems to be complete. Second remissions were never very satisfactory in our cases after readministration of hormone therapy. Of the 14 cases in which an attempt was made to produce a second hormone remission, a partial response was observed in 6 and none whatever in the remainder.

An analysis of the effectiveness of folic acid antagonist therapy in the different types of acute leukemia, comparable to the present one, has not been published. In many of the reported series, the morphologic type was not given. In a total of 112 reported cases for which such data are available * "complete" and partial remissions were observed in 45% of 49 cases of the lymphoblastic type, in 27% of 48 cases of myeloblastic leukemia, and in 26% of 15 cases of monoblastic leukemia. Wilson's series of 70 cases [36] includes such an unusually high proportion of cases of monoblastic leukemia that this series should be mentioned separately. He observed remissions in 53% of 38 cases of lymphoblastic leukemia, in none of 4 cases of myeloblastic leukemia, and in 43% of 23 cases of monoblastic leukemia.

The results of a deliberate study of a substantial number of cases in a single clinic would probably be more significant than a compilation from the literature. Our own series of cases treated with a folic acid antagonist alone is too small to have value. Dameshek and associates [33] reported 32 cases in which there was an adequate trial. Remissions occurred in 43% of the lymphoblastic cases, in 27% of the myeloblastic cases, and in none of the monoblastic leukemias. Three cases were not classified. A remission was observed in one of these. Thus it would seem, from these limited data, that the responsiveness of acute lymphoblastic leukemia to treatment with folic acid antagonists is greater than that of the other types of acute leukemia. The difference, however, is not as striking as we have found with hormone therapy; nor has there been any indication of acceleration of the disease process by therapy.

If our observations are correct, it follows that a serious attempt should be made to differentiate the various types of acute leukemia before a decision is made concerning therapy. In cases of the lymphoblastic type, the use of cortisone may be expected to bring about a remission promptly in the great majority of cases. In the myeloblastic and monoblastic varieties such therapy is not helpful and may

* References 29-35.

be harmful; treatment with a folic acid antagonist may be preferable. In such cases, another type of antagonist, 6-mercaptopurine,[37] also deserves a trial.

SUMMARY

A study has been made of the effectiveness of hormone therapy in 47 cases of acute leukemia. Excellent results were observed in the lymphoblastic variety, complete remissions occurring in 18 out of 22 children (82%) 10 years of age and under and in 3 out of 9 older patients. Partial remissions were described in another seven cases. There were only three failures.

In contrast, complete remissions were not observed among 15 cases of acute myeloblastic leukemia, and there were only 2 partial remissions. This form of treatment also failed in a case of acute monocytic leukemia. In some of these cases treatment seemed to accelerate the leukemic process.

These observations suggest that hormone therapy should be reserved for the lymphoblastic variety of acute leukemia and that, in the other forms of acute leukemia, such therapy may even be contraindicated.

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CARBOHYDRATE METABOLISM IN BRAIN DISEASE

II. Glucose Metabolism in Schizophrenic, Manic-Depressive, and Involutional Psychoses

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THE NATURE, extent, and significance of changes in carbohydrate metabolism in schizophrenia and in manic-depressive and involutional psychoses have long been controversial subjects.[1] The experiments described here were designed to throw light on these questions about the carbohydrate metabolism in psychotic patients.

MATERIAL AND METHODS

The subjects studied were psychotic patients and normal adult subjects of comparable age. The psychotic patients were suffering from schizophrenic, manic-depressive, or involutional psychoses; had no other intercurrent disease; were well nourished and not debilitated; were not receiving shock therapy, and were cooperative during the study; the women had normal menstrual function. All subjects had a high carbohydrate intake, in addition to their adequate normal diets, for three to five days before each experiment. They were at rest throughout the study and in the fasting state at the time the initial blood specimen was taken.

The methods used were that of Folin and Wu for blood glucose,[2] that of Somogyi for the preparation of the blood filtrate for the determination of true blood glucose,[3] that of Fiske and Subbarow for serum inorganic phosphate,[4] that of Friedemann and Haugen for the nonchromatographic measurement of blood pyruvic acid,[5] that of Barker and Summerson for blood lactic acid,[6] that of Taussky and Shorr for plasma citric acid,[7] and that of Seligson and Shapiro for the chromatographic determination of pyruvic acid and α-ketoglutaric acid.[8] Adequate precautions in the preservation of the blood for subsequent determinations of lactic, pyruvic, and α-ketoglutaric acids were taken, as outlined by Friedemann and Haugen.[9] The methods used under the conditions of our laboratory were reproducible within a range of ± 1.5% between duplicate samples, except in the case of plasma citric acid, where a variation of ± 3.5% obtained. Urine inorganic phosphate and citric and lactic acid concentrations were determined by slight modifications of the techniques used on the blood specimens.

In one group of studies the subjects ingested 100 gm. of glucose dissolved in 200 cc. of distilled water over a five-minute interval; blood specimens were taken in the fasting state, and one, two, and three hours after the ingestion of the glucose. In a second group of studies 50 gm. of dextrose dissolved in a liter of isotonic sodium chloride solution was given intravenously over either a half-hour or a two-hour interval; specimens were drawn at the same time as during the oral administration of glucose, with the addition of one drawn 30 minutes after the start of the infusions.

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In the studies of urinary components, urine specimens were collected at timed hourly intervals, after the specimen voided on awakening was first collected and discarded. The first three samples showing constant phosphate- and lactic- and citric-acid-excretion rates served as the control specimens for that day's experiment. The one-, two-, and three-hour urine specimens immediately following the start of the study served as the test samples for that same day's study.

In an attempt to correlate the clinical status of the acute patient with the chemical abnormalities, tests were performed before and after the treatment whenever possible. The first study was made within the first week after admission to the hospital, and the second test was made at least two weeks after the last insulin or electric shock treatment.

OBSERVATIONS

A. Fasting Values.—In the normal subjects, the fasting blood levels of glucose, all the measured carbohydrate breakdown products, and the serum inorganic phosphate were within the ranges established in the literature by those using the same methods (Table). No differences between the psychotic and the nonpsychotic sub-

Fasting Values for Blood Constituents in Normal Subjects and Psychotic Patients

	Normal Subjects			Psychotic Patients		
	Mg./100 Ml.			Mg./100 Ml.		
	Range	Mean	No. Cases	Range	Mean	No. Cases
Total reducing substance (Folin-Wu)	80-120 *	100 *	..	72-112	90	23
True glucose (Somogyi; Folin-Wu)	60-88	74	21	56-108	79.3	83
Whole blood lactic acid	2.75-11.6	7.40	26	2.50-18.0	8.1	85
Whole blood pyruvic acid (chemical method)	0.7-2.75	1.50	30	0.6-2.45	1.50	36
Whole blood pyruvic acid (chromatographic method)	0.520-1.32	0.920	12	0.15-1.25	0.720	16
Plasma citric acid	1.6-3.6	2.34	27	1.25-3.70	2.22	40
Whole blood α-ketoglutaric acid (chromatographic method)	0.080-0.116	0.110	12	0.015-0.27	0.123	16
Total serum inorganic phosphate	3.46-4.20	3.77	21	3.0-4.6	3.78	101

* These values given in the literature.

jects were found, except with respect to the true blood glucose and the whole blood lactic acid concentrations. Forty-one per cent of the patients had fasting true blood glucose concentrations higher than two standard deviations from the normal mean. Thirty-five per cent of the patients showed blood lactic acid levels higher than 10 mg. per 100 ml., whereas only 1 of the 26 normal subjects studied here had a fasting lactic acid concentration above 10 mg. per 100 ml. The values shown in the Table are the combined observations made in patients with psychoses of recent onset and those with chronic psychoses.

B. Metabolic Effects of Oral Administration of Glucose.—The changes in the true blood glucose in the normal subjects after the oral administration of glucose confirmed reports in the literature.* In the psychotic patients, there was a delay in the return of the glucose level to the fasting concentration: In 11 of the 13 patients with psychosis of recent onset and in 6 of the 9 with chronic psychosis the blood glucose concentration was above the control level two hours after ingestion of the glucose (Fig. 1). In half of the patients with psychosis of recent onset the level was still above the fasting level at three or four hours. Of the eight patients

* Cantarow and Trumper,[10] p. 38.

studied after treatment, those who showed clinical remission also exhibited improvement in glucose tolerance; clinical relapse, or failure to improve with treatment, was associated with persistence of the impaired glucose tolerance.

The 1 to 3 mg. rise in blood lactic acid concentration observed in the normal subjects confirms the findings already established in the literature.[11] An excessive and prolonged rise in whole blood lactic acid after the oral administration of glucose was observed in the psychotic patients (Fig. 2). This metabolic observation was seen almost exclusively in the patients with psychosis of recent onset; only one of seven patients with chronic psychoses had an increased elevation of the blood lactic acid level after the ingestion of glucose. A favorable response to treatment was associated with the exhibition of a normal change in blood lactic acid level after

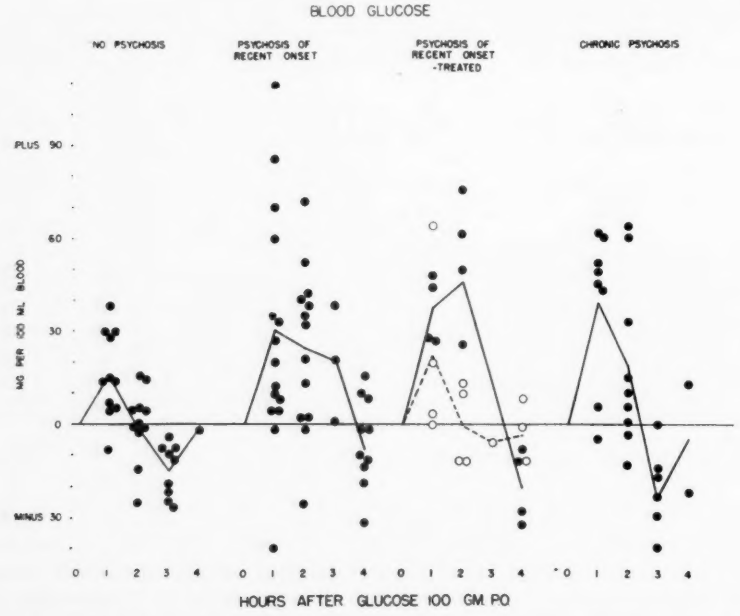
BLOOD GLUCOSE
NO PSYCHOSIS
PSYCHOSIS OF RECENT ONSET
PSYCHOSIS OF RECENT ONSET -TREATED
CHRONIC PSYCHOSIS
PLUS 90
60
30
0
MINUS 30
MG PER 100 ML. BLOOD
0 1 2 3 4 0 1 2 3 4 0 1 2 3 4 0 1 2 3 4
HOURS AFTER GLUCOSE 100 GM. PO.

Fig. 1.—Changes in true blood glucose concentration after ingestion of 100 gm. of glucose. Open circles refer to patients improved after treatment. Lines indicate average changes, the broken line indicating average changes in patients improved after treatment.

ingestion of glucose; an unfavorable response to therapy, or clinical relapse, was associated with the persistence of the abnormally large increases in lactic acid concentration after the oral administration of glucose (Fig. 2).

The changes in blood pyruvic acid concentration in the normal subjects after the ingestion of glucose were similar to those previously reported by other investigators;† some normal subjects showed a fall one hour after taking glucose (Figs. 3 and 4). The changes in blood pyruvic acid concentration in the psychotic patients overlapped those of the normal subjects considerably, but the averages differed. There was an increased and prolonged accumulation of pyruvic acid whether meas-

† References 12 and 13.

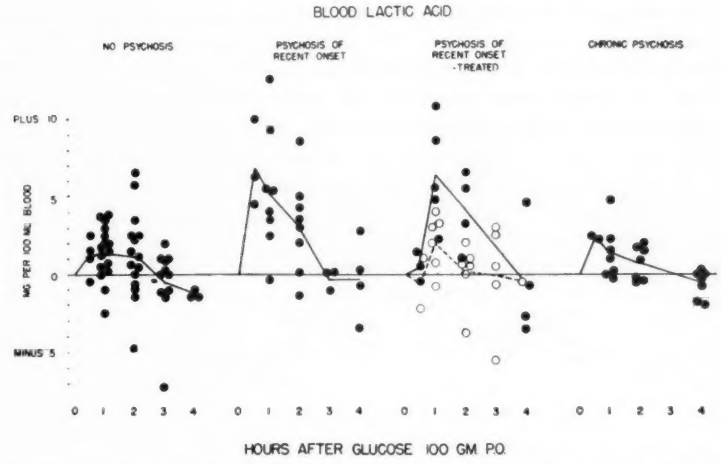
BLOOD LACTIC ACID
NO PSYCHOSIS
PSYCHOSIS OF RECENT ONSET
PSYCHOSIS OF RECENT ONSET -TREATED
CHRONIC PSYCHOSIS
PLUS 10
5
0
MINUS 5
MG PER 100 ML BLOOD
0 1 2 3 4 0 1 2 3 4 0 1 2 3 4 0 1 2 3 4
HOURS AFTER GLUCOSE 100 GM P.O.

Fig. 2.—Changes in blood lactic acid concentration after ingestion of 100 gm. of glucose. Open circles refer to patients improved after treatment. Lines indicate average changes, the broken line indicating average changes in patients improved after treatment.

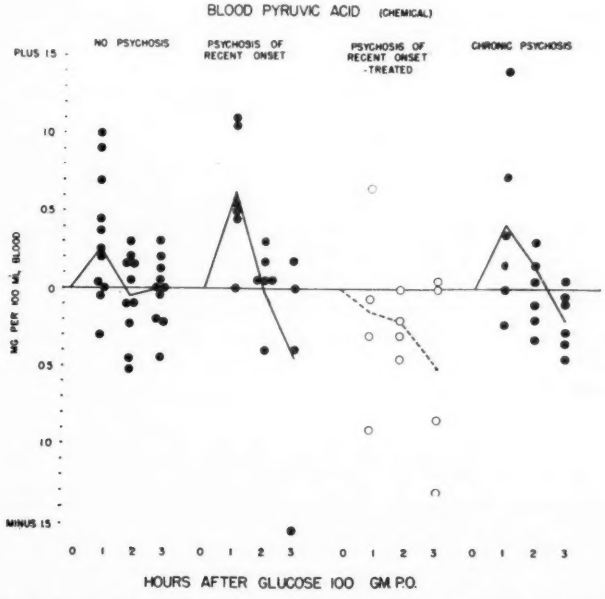

Fig. 3.—Changes in blood pyruvic acid concentration (chemical method used) after ingestion of 100 gm. of glucose. Open circles refer to patients improved after treatment. Lines indicate average changes, the broken line indicating average changes in patients improved after treatment.

ured by the nonchromatographic [5] or the chromatographic [8] technique (Figs. 3 and 4). When the nonchromatographic technique was used, the average increase above the mean fasting concentration one hour after the ingestion of glucose was 19% in the normal subjects and 46% in the patients with psychoses of recent onset. When the chromatographic technique was used, the average increase above the mean fasting concentration one hour after the ingestion of the glucose was 11%

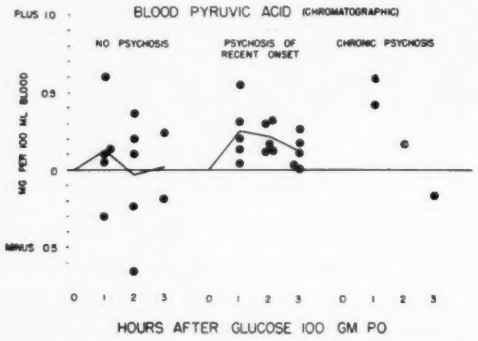

Fig. 4.—Changes in blood pyruvic acid concentration (chromatographic method used) after ingestion of 100 gm. of glucose. Lines indicate average changes.

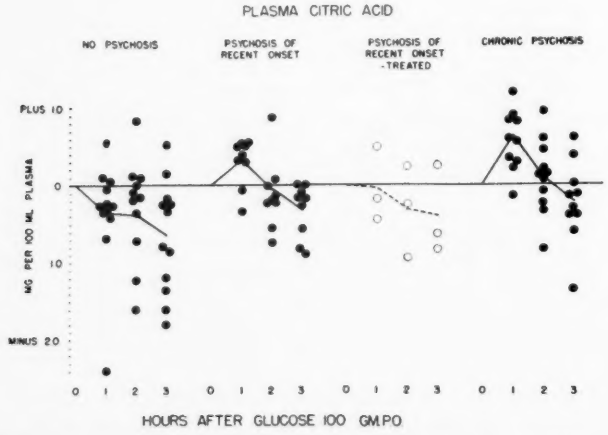
PLASMA CITRIC ACID
NO PSYCHOSIS
PSYCHOSIS OF RECENT ONSET
PSYCHOSIS OF RECENT ONSET -TREATED
CHRONIC PSYCHOSIS
PLUS 1.0
MG PER 100 ML. PLASMA
0
1.0
MINUS 2.0
0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3
HOURS AFTER GLUCOSE 100 GM PO

Fig. 5.—Changes in plasma citric acid concentration after ingestion of 100 gm. of glucose. Open circles refer to patients improved after treatment. Lines indicate average changes, the broken line indicating average changes in patients improved after treatment.

for the normal subjects and 51% for the patients with psychoses of recent onset. The findings two or three hours after the ingestion of glucose were normal (Figs. 3 and 4). Of the four patients studied after clinical remission, one still showed an excessive increase in pyruvic acid concentration one hour after the oral administration of glucose, whereas three showed a fall in pyruvic acid concentration after

one hour. The patients with chronic psychoses showed an increased average rise in the blood pyruvic acid curve after ingesting glucose, but here, too, there was much overlap with the normal values.

Studies of plasma citric acid concentration after the ingestion of glucose showed that 1 of the 12 normal subjects had a significant rise at one hour (Fig. 5); in the remaining 11 there was the normal steady fall previously reported by others.[14] The changes in plasma citric acid in the psychotic patients were strikingly abnormal. In 7 of the 9 patients with psychosis of recent onset, and in 9 of the 10 with chronic psychosis, the plasma citric acid concentration rose one hour after the oral administration of glucose (Fig. 5). This rise was still present in many of the chronically psychotic patients two and three hours after the ingestion of glucose. The effect of clinical remission in the three patients studied was variable; there was persistence of the abnormal rise in one and the appearance of normal fall in two (Fig. 5).

The changes in blood α-ketoglutaric acid concentration observed after the oral administration of glucose were qualitatively similar to those observed in plasma

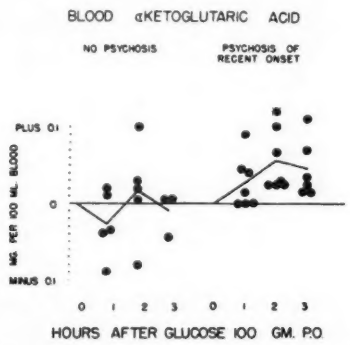

Fig. 6.—Changes in blood α-ketoglutaric acid concentration after ingestion of 100 gm. of glucose. Lines indicate average changes.

citric acid level. One hour after the ingestion of the glucose the α-ketoglutaric acid concentration fell in the normal subjects and rose in the psychotic patients (Fig. 6). The elevation in blood level observed in the psychotic patients persisted throughout the test period, in contrast to the findings in the normal subjects, who usually showed either no significant change or a fall two and three hours after the ingestion of glucose.

The fall in serum inorganic phosphate level that occurred in the normal subjects after the ingestion of glucose was within the range described by others for normal subjects.‡ In the patients with psychosis of recent onset there was an increased and prolonged fall in serum inorganic phosphate after the ingestion of the 100 gm. of glucose in comparison with that observed in the normal group (Fig. 7); the abnormal changes in inorganic phosphate concentration became normal upon clinical remission, but clinical relapse or failure to respond to treatment was associated with a persistence of this biochemical abnormality. This abnormality was not observed in the patients with chronic psychoses (Fig. 7).

‡ Cantarow and Trumper,[10] p. 18.

C. Urinary Excretion of Inorganic Phosphate and of Lactic and Citric Acids After Oral Administration of Glucose.—The urinary excretion of inorganic phosphate and of lactic and citric acids in 6 normal subjects and 13 psychotic patients, measured for three hours before and three hours after the ingestion of 100 gm. of glucose, showed much variation. There was no consistent or significant difference between the normal and the psychotic groups. In both groups the oral administration of glucose did not raise the excretion rate of lactic acid above that of the control period. The excretion of phosphate and citrate did not change to values appreciably above or below the control rates in either the normal or the psychotic subjects.

D. Metabolic Effects of Intravenously Administered Dextrose.—1. Fifty Grams Infused Intravenously in 30 Minutes: When 50 gm. of dextrose was infused over a half-hour period,[15] the metabolic changes observed in the normal subjects and the

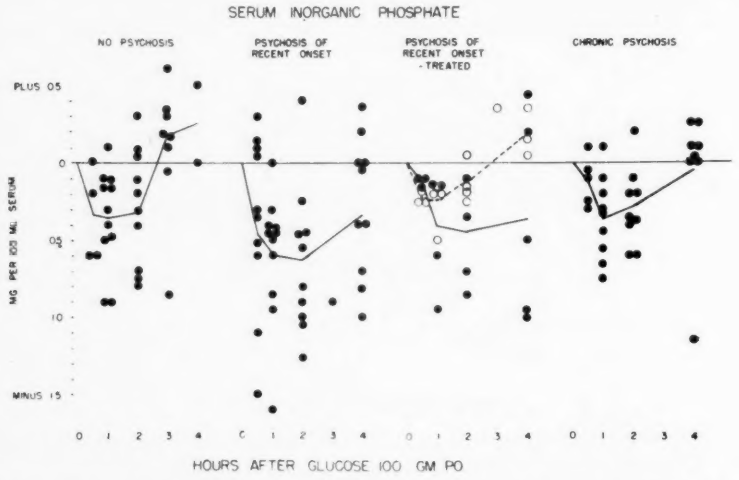

Fig. 7.—Changes in serum inorganic phosphate concentration after ingestion of 100 gm. of glucose. Open circles refer to patients improved after treatment. Lines indicate average changes, the broken line indicating average changes in patients improved after treatment.

psychotic patients were similar. In the normal group the mean glucose concentration one hour after 50 gm. of dextrose was administered intravenously in 30 minutes was nine times greater than the mean glucose concentration one hour after 100 gm. administered orally (Figs. 1 and 8). No significant difference in the glucose tolerance between the normal and psychotic patients was observed (Fig. 8). In the 5 normal subjects and the 20 psychotic patients, 7 of whom had chronic psychoses, the blood glucose concentration was at or below the fasting concentration by two hours after the start of the infusion, except in 3 of 13 patients with psychosis of recent onset.

In the normal subjects the rise in blood lactic acid after the administration of 50 gm. of dextrose by vein was considerably higher than that observed after 100 gm. of glucose by mouth (Figs. 2 and 9). The change in blood lactic acid observed in the psychotic patients was similar to that seen in the normal subjects. The results

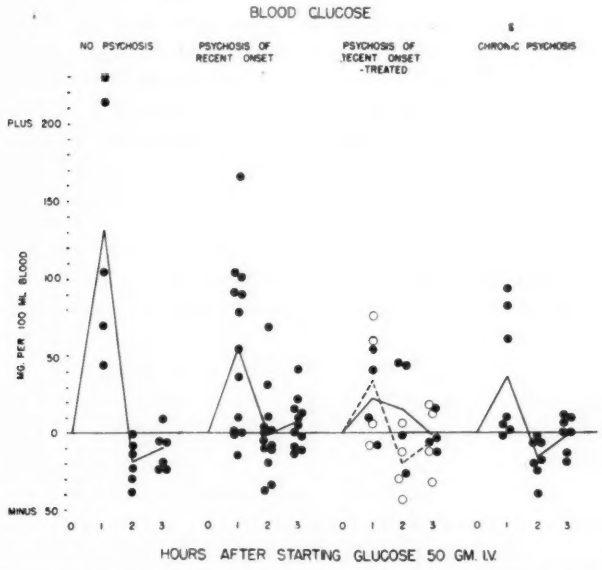

Fig. 8.—Changes in true blood glucose concentration after intravenous infusion of 50 gm. of dextrose in 30 minutes. Open circles refer to patients improved after treatment. Lines indicate average changes, the broken line indicating average changes in patients improved after treatment.

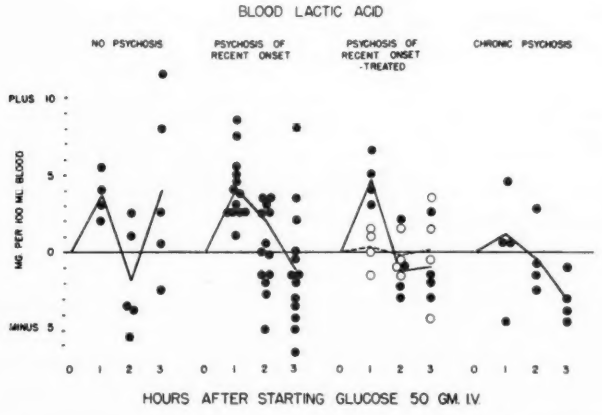
BLOOD LACTIC ACID
NO PSYCHOSIS
PSYCHOSIS OF RECENT ONSET
PSYCHOSIS OF RECENT ONSET -TREATED
CHRONIC PSYCHOSIS
PLUS 10
5
0
MINUS 5
MG. PER 100 ML. BLOOD
0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3
HOURS AFTER STARTING GLUCOSE 50 GM. I.V.

Fig. 9.—Changes in blood lactic acid concentration after intravenous infusion of 50 gm. of dextrose in 30 minutes. Open circles refer to patients improved after treatment. Lines indicate average changes, the broken line indicating average changes in patients improved after treatment.

of treatment in the patients with psychosis of recent onset appeared to influence the lactic acid changes; clinical remission was associated with a decreased accumulation of lactic acid after the injection of dextrose (Fig. 9).

Changes in blood pyruvic acid concentration after the injection of 50 gm. of dextrose in one-half hour were variable in the normal subjects; the changes seen in the psychotic patients were within the same range (Fig. 10).

In both the normal subjects and the psychotic patients the changes in plasma citric acid concentration after the infusion of the dextrose in one-half hour were variable (Fig. 10). In the five normal subjects studied, two had a rise of 0.20 and 1.10 mg. per 100 ml. at one hour, with a subsequent steady fall; two had a steady fall throughout the test period, and one showed no change. Others have reported a steady fall.§ In the three psychotic patients studied (one of whom had a chronic psychosis), two had a rise of 0.11 mg. per 100 ml. and 0.2 per 100 ml., respectively, at one hour, with a subsequent fall, and one had a steady fall from the fasting concentration throughout the test period (Fig. 10).

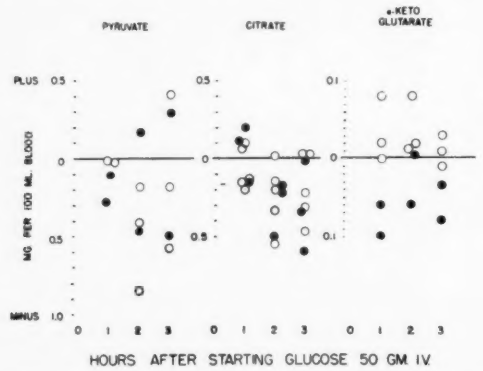

Fig. 10.—Changes in blood pyruvic, citric, and α-ketoglutaric acid concentrations after intravenous infusion of 50 gm. of dextrose in 30 minutes. Open circles refer to normal subjects; dots refer to patients.

The normal subjects showed rises in blood α-ketoglutaric acid concentration similar to those reported by other observers,[18] who also studied these changes after the rapid intravenous infusion of dextrose. However, the psychotic patients studied here all showed no change or decreases (Fig. 10).

The normal subjects showed changes in serum inorganic phosphate concentration similar to those reported by others who studied normal subjects in this way: the normal response is a maximal fall in serum inorganic phosphate concentration of 12 to 25% at two to two and one-half hours.[19] The changes in serum inorganic phosphate concentration observed in the 26 psychotic patients studied showed a 16 to 19% fall one-half to two hours after the start of the infusion, with a mean maximum fall of 0.57 mg. per 100 ml.

2. Fifty Grams Infused Intravenously in Two Hours: When 50 gm. of dextrose was infused intravenously over a two-hour period in four normal subjects and in

§ References 16 and 17.

six psychotic patients who had previously shown abnormal metabolic response to 100 gm. of glucose by mouth, the changes in blood glucose and pyruvic acid concentrations were not significantly different in the two groups (Fig. 11). However, all six of the psychotic patients (two of whom had chronic psychoses) showed abnormally increased and prolonged elevations of blood lactic acid concentration after receiving the dextrose. In addition, all six patients showed rises in plasma citric acid concentration after one-half to one hour following the start of the infusion, instead of the normal slight fall (Fig. 11).

E. Changes in Blood Eosinophile Count Induced by Tolerance Tests.—Five normal subjects showed insignificant changes in blood eosinophiles after ingesting 100 gm. of glucose. In 16 psychotic patients the oral administration of glucose similarly caused no significant change in the concentration of blood eosinophiles four hours after the start of the glucose-tolerance test; no patients had a fall greater

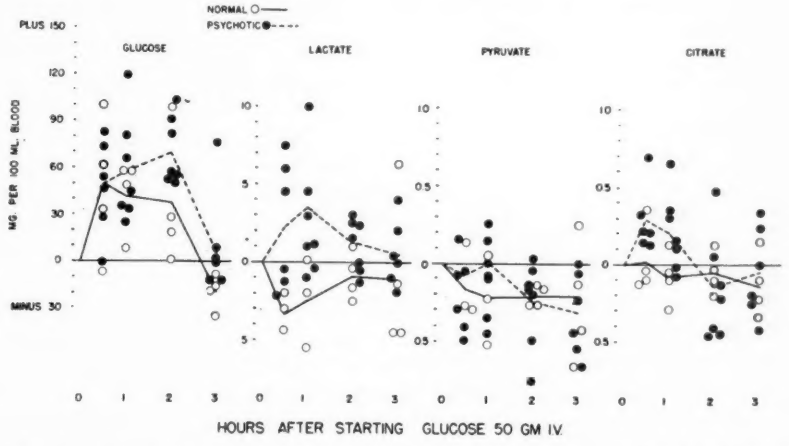

Fig. 11.—Changes in true blood glucose and in blood lactic, pyruvic, and citric acid concentrations during and after intravenous infusion of 50 gm. of dextrose in two hours. Open circles refer to normal subjects; dots refer to patients. Solid lines indicate average changes in normal subjects; broken lines indicate average changes in patients.

than 40% from the fasting concentration. Of the 17 subjects receiving dextrose by vein, none showed a decrease in blood eosinophiles greater than 50%, although others have reported a fall.[20]

COMMENT

Earlier work by many workers [1] indicated that the rise in the glucose level after the ingestion of glucose is often abnormally high in patients with the psychoses under consideration here. The bulk of this earlier work is open to criticism, in that malnutrition was not ruled out and the patients studied had not been given a high-carbohydrate diet before the tests were made. Indeed, it is assumed by some that metabolic abnormalities observed in manic-depressive, involutional, or schizophrenic psychoses are due to debility or malnutrition. These factors can be ruled out in the psychotic patients studied here. All subjects studied were well-nourished and were cooperative regarding the pretest high-carbohydrate diet.[21]

Observations on blood glucose alone afford a most incomplete view of carbohydrate metabolism. Only fragmentary additional findings in psychotic patients are recorded in the earlier literature; they consist in a few reports of abnormally high fasting blood lactic acid concentration and excessive rises in blood lactic acid and decreases in serum inorganic phosphate levels after the ingestion of carbohydrate.‖ These observations have been confirmed and extended here. In addition, other blood carbohydrate fractions were studied here, and so the disorder of carbohydrate metabolism that occurs in patients with schizophrenic, manic-depressive, and involutional psychoses may now be described more fully: the fasting blood concentrations of pyruvic, citric, and α-ketoglutaric acids and of inorganic phosphate are usually normal; the fasting blood glucose and lactic acid concentrations are frequently elevated. Following the ingestion of glucose by patients with psychoses of recent onset, excessive rises in blood glucose and blood lactic and pyruvic acid concentrations occur; blood citric and α-ketoglutaric acid levels usually show an early rise instead of the normal steady fall; serum inorganic phosphate concentrations show excessive decreases. Every patient studied exhibited at least three of these abnormalities, and many exhibited all. The observed abnormalities usually disappeared after successful treatment, but they persisted or became more marked in patients unimproved or in relapse after treatment. The development of the chronic state is associated with a worsening of the abnormal changes in blood citric and α-ketoglutaric acid concentrations after ingestion of glucose. On the other hand, the abnormalities in the changes in blood lactic acid and serum inorganic phosphate concentrations usually disappeared. These differences suggest that perhaps more than one disorder of intermediary carbohydrate metabolism is present in patients with psychoses of recent onset.

The nature of the fundamental metabolic aberration or aberrations responsible for the abnormalities found here cannot be stated. Insulin deficiency is ruled out, for the findings in diabetes mellitus consist in little or no rise in blood lactic and pyruvic acid concentrations or fall in serum inorganic phosphate levels after ingestion of glucose.¶ Thiamine deficiency is ruled out by the histories of the patients. The biochemical aberrations observed in the patients studied here did not vary with the type of psychosis nor could they be correlated with the thought content, state of mind, or condition of the mood in the patients. Anxiety and the consequent sympathetic discharge was not a factor: sham experiments in which nothing was administered but water by mouth, and in which repeated blood samplings were made, showed no changes resembling those observed in the actual tests; moreover, changes in blood eosinophile count were not significant in either the sham experiments or in the actual tolerance tests.[20] Starvation has been ruled out, as described above, by the choice of patients and the use of a high-carbohydrate diet prior to the tests. It should be borne in mind, however, that severe starvation in normal man causes fasting hyperglycemia and hyperlacticacidemia and that following ingestion of glucose there is a lag in the return of the blood glucose to fasting concentrations, an excessive rise in blood pyruvic acid concentration, and a rise rather than a fall in plasma citric acid level.# Like well-fed psychotic patients,* starving normal men

‖ References 22-24.
¶ References 13, 25, and 26.
# References 27 and 28.
* References 1 and 29.

also exhibit high fasting blood ketone levels and manifest insulin resistance.[27] These biochemical similarities between the starving normal man and the well-fed psychotic patient should be studied further. These same abnormalities have been reported to occur in rabbits following the subcutaneous injection of acetoacetate.† The relation of these studies to starvation and to mental disorders is not known; all three manifest increased ketosis.

The question of some type of impairment of hepatic function being the cause of the abnormalities of carbohydrate metabolism found must be considered. It was hoped that the use of a standard intravenous glucose-tolerance test might be helpful in this respect. The observations made here showed no difference between normal and psychotic subjects when 50 gm. of dextrose was given intravenously in 30 minutes; this finding might be taken to indicate that by-passing the liver abolishes the disordered carbohydrate metabolism of psychosis. However, this idea was negated by the fact that giving 50 gm. of dextrose intravenously in two hours gave rise to most of the abnormalities seen after the oral ingestion of 100 gm. of glucose, but to a lesser degree. The assumption that 50 gm. of dextrose given in 30 minutes is equivalent as a test load to 100 gm. given by mouth [15] is not valid; the two tests are equivalent only if the return of the glucose concentration to the fasting level at two hours is made the criterion. The changes observed in normal subjects after administration of 50 gm. of dextrose by vein in a half hour differ from those observed after the administration of 100 gm. of glucose by mouth; in the former there is a greater rise in blood glucose and lactic acid concentration at one hour and a rise or only a slight fall in plasma citric acid level. The reasons for these differences are unknown; a possible explanation might be that, when administered by mouth, large portions of the glucose are phosphorylated by the intestinal mucosa,[33] a process which perhaps accelerates the subsequent utilization of the glucose. The reason why the psychotic patients showed changes similar to those of the normal subjects when given 50 gm. of dextrose intravenously in 30 minutes but not in 2 hours is unknown. The rate of infusion is obviously the determining factor in this phenomenon, but much additional study will be required to explain the findings.

The excessive fall in serum inorganic phosphate concentration after ingestion of glucose is not due to abnormal excretion of that ion in the urine. Our normal and psychotic subjects both showed only insignificant changes in urinary phosphate after glucose by mouth. A curious phenomenon found here was the simultaneous occurrence of impaired intermediary carbohydrate metabolism and of an excessive fall in serum inorganic phosphate concentration after administration of glucose. Previous investigators, who studied mainly diabetes and insulin action, designated a failure of serum inorganic phosphate concentration to decrease after administration of glucose as evidence of impaired intermediary carbohydrate metabolism.‡ This idea evidently should be reexamined.

The similarity of the abnormalities observed after ingestion of glucose in patients with multiple sclerosis [34] and in those with the psychoses discussed here is striking. In both diseases there is a lag in the return to fasting blood glucose concentration, increased elevations of blood lactic and pyruvic acids, and a fall rather than the

† References 30-32.

‡ Cantarow and Trumper,[10] p. 192.

normal rise in plasma citric acid concentration after ingestion of 100 gm. of glucose. Similar abnormalities have been described in patients with other neurologic syndromes.[17] The abnormal intermediary carbohydrate metabolism exhibited by patients with schizophrenic, manic-depressive, and involutional psychoses is evidently not the primary cause of these conditions. On the other hand, the findings suggest that these psychoses are organic diseases of the brain.

SUMMARY AND CONCLUSIONS

Studies of carbohydrate metabolism in the fasting state and after administration of glucose have been made in patients with schizophrenic, manic-depressive, and involutional psychoses. The fasting blood concentrations of pyruvic, citric, and α-ketoglutaric acids and of inorganic phosphate are normal; one-third of the patients show significant elevations of true blood glucose and lactic acid concentrations.

Changes observed in the patients after the ingestion of 100 gm. of glucose overlap those found in the normal subjects, but there are significant differences in the changes in all blood constituents measured: in the psychotic patients there is a lag in the return to the fasting level of the true blood glucose, an excessive elevation in lactic and pyruvic acids, a rise rather than a fall in citric and α-ketoglutaric acids, and an increased and prolonged fall in serum inorganic phosphate. Clinical status can be correlated with biochemical abnormality: patients with psychosis of recent onset manifest at least three and frequently all of the abnormalities, whereas those with chronic psychosis fail to exhibit the abnormal changes in blood lactic acid and inorganic phosphate but usually show the citric and α-ketoglutaric acid changes to an exaggerated degree. Remission following treatment is correlated with biochemical changes toward the normal values.

The intravenous infusion of 50 gm. of dextrose in a two-hour period in normal and psychotic subjects shows differences similar to those seen after the ingestion of 100 gm. of glucose. However, when the 50 gm. of dextrose are infused rapidly in a one-half hour period, the normal and psychotic subjects show comparable changes. The reason for this effect of the rate of infusion of dextrose is unknown; although the half-hour infusion of 50 gm. of dextrose is comparable to the ingestion of 100 gm. of glucose in normal subjects if only changes in blood glucose concentration are measured, the two tests are found not to be comparable if changes in breakdown products of glucose are measured.

The relation of the biochemical abnormalities observed after glucose administration in patients with psychosis to those observed in starvation, to those found in other organic brain diseases, and to abnormal ketosis is discussed. Data presented here indicate that patients with the psychoses studied show measurable biochemical abnormalities remarkably similar to those observed in patients with organic brain disease.

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EMETIC ACTION OF ETHYL ALCOHOL

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THAT INGESTED ethyl alcohol is possessed of an emetic action is well recognized by scientist and layman alike. Indeed, on a purely numerical basis, emesis from alcohol in man must be much more frequent than that from any other agent. Yet search of the literature is not successful in bringing to light any experimental work on the subject either in man or in lower animals. When accorded casual mention, it is generally assumed that the action is a local one on the gastrointestinal tract and that the type of beverage is of considerable importance.

It was thus of great interest to us to find that a considerable number of persons vomited after intravenous injection of doses of alcohol well within the range of ordinary social intake. For this reason, in the course of numerous experiments in which alcohol was administered to human subjects by both oral and intravenous routes we have recorded the incidence of emesis, and it is the purpose of this communication to present the data so obtained.

EXPERIMENTAL METHOD

The subjects were of both sexes, free of obvious disease of the gastrointestinal system. They varied in age from 16 to 60, and there was no selection in regard to alcoholic habits. All were fasting for a period of three hours prior to the experiment. When administered intravenously, alcohol was diluted to 10% by volume, and a dose equivalent to 1.00 cc. of absolute alcohol per kilogram of body weight was injected into a vein in the cubital fossa by gravity at a constant rate in one hour. Determination of blood alcohol concentration in venous blood from the opposite arm during and after the injection showed the maximum to be reached at the end of the injection, followed by a slow decline at an essentially constant rate. When administered orally, either alcohol or whiskey was diluted to taste with plain or carbonated water, cooled with ice, and a dose of 0.2 cc. per kilogram was given each 20 minutes until failure on a test of balance occurred. Blood alcohol determinations were made before and after failure on the test, so that the maximum concentration achived could be determined. Careful records were kept of emesis, if it occurred, and of other symptoms shown by the subject. Alcohol determinations were made on venous blood by the methods of Newman [1] and Newman and Newman.[2]

RESULTS

Thirty-seven experiments were performed on the same number of subjects by the intravenous route. Maximum blood alcohol concentrations varied from 81 to 137 mg. per 100 cc., the average being 107 mg. There were nine instances of emesis,

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four shortly before or at the end of the injection and the remainder within two hours. The average maximum blood alcohol concentration in those subjects who vomited was 118 mg., contrasted with 103 mg. in those who did not.

Twenty experiments were performed on seven subjects by the oral route. Maximum blood alcohol concentrations varied from 69 to 180 mg. per 100 cc., with an average of 123 mg. Emesis occurred in six experiments, but all but two subjects vomited on one or another occasion. The average blood alcohol concentration when emesis occurred was 123 mg.; in cases in which emesis did not occur, it was 124 mg. While in general the same person was more likely to vomit with a higher blood alcohol concentration, this was not always the case. Thus, one subject did not vomit on two occasions when the maximum concentration was 175 mg. but did so once when it was 172 mg. Again, a subject who did not vomit when the concentration was 126 mg. did so when it was 113 mg.

COMMENT

The incidence of emesis after intravenous administration of alcohol was 24%, while after oral administration it was 30%. Since the average maximum blood alcohol concentration reached was lower in the intravenous series, namely, 107 mg. per 100 cc. compared with 123 mg., it would seem apparent that there is no significant difference in the emetic activity of a given blood alcohol concentration achieved by the two routes. When alcohol is given intravenously, the maximum concentration in the gastric secretion cannot be expected to exceed that in the blood plasma, while with oral administration the concentration in the gastric contents may approximate that in the beverage ingested. Thus, if the emetic action of alcohol were local, in the stomach, one would expect a tremendously greater incidence of emesis after oral administration. The data presented constitute strong evidence that the action is not a local one.

Whether vomiting from alcohol is due to direct stimulation of the emetic center or is reflex from some other nervous structure, we are not presently able to state. It is of interest, however, that at about the same levels of alcohol concentration at which emesis occurs the subjects frequently complained of vertigo and diplopia, and nystagmus was observed in several. The loci for all these phenomena lie not far distant from the emetic center in the brain stem.

Equally interesting was the fact that, in the subjects given alcohol by mouth, emesis occurred at about the same blood alcohol concentration at which obvious evidence of deterioration in nervous system function, as evidenced by loss of balance and slowing of the electroencephalogram, became apparent. That all but two of these subjects vomited on one occasion or another at the point in the blood alcohol curve at which changes in these tests of nervous function became obvious indicates that, under the circumstances of the experiment, with a slowly rising blood alcohol concentration, most persons will vomit before a stage of intoxication which grossly interferes with consciousness and locomotion is attained. No doubt this attribute of alcohol contributes to its relative safety so far as death from acute toxicity is concerned, since the onset of emesis can generally be depended on to limit intake, under ordinary circumstances of usage, to nonfatal levels.

SUMMARY

The incidence of emesis was essentially similar when alcohol was given to human subjects orally or intravenously. From this it is concluded that the emetic action of alcohol is not exerted locally on the gastrointestinal tract but rather is exerted on the emetic center either directly or by reflex from some other nervous structure or structures.

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MANAGEMENT OF ANORECTAL COMPLICATIONS OF CHRONIC ULCERATIVE COLITIS

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THE PURPOSE of this paper is not to point out when an ileostomy should or should not be performed in cases of chronic ulcerative colitis but to discuss the proper management of the anorectal complications of the disease and thus obviate performing an ileostomy or colectomy or both of these operations, at least in some cases. Just where to draw the line between medical or conservative management and surgical treatment of chronic ulcerative colitis and its complications is a matter of individual judgment. There is a wide disparity of opinion among surgeons and internists as to when surgical treatment should be instituted. On the one hand are those who advocate the use of ileostomy and colectomy early in the disease. In general, it is our feeling at the Mayo Clinic that radical operation should be performed only in those cases in which the disease cannot be controlled medically or in cases in which certain complications develop. Even so, with this conservative or middle-of-the-road attitude, it is frequently difficult to exercise proper judgment.

Since the commonest complications of chronic ulcerative colitis occur in the anorectal region, the proctologist is frequently called on to exercise his judgment in the proper method of dealing with the local complication. Since chronic ulcerative colitis begins in the rectum and progresses proximally, the disease is present in the rectum for a longer time than it is in the more proximal segments of the intestine. Therefore, it is understandable why the rectum is the most frequent site of complications of the disease.

MATERIAL

This report is based on 200 consecutive cases of chronic ulcerative colitis in which the patients were observed at the Mayo Clinic. One hundred twenty-one of the patients were males, and 79 were females. Anorectal complications occurred in 32 (16%) of the 200 cases. Multiple complications were the rule rather than the exception. A good many of the patients not only had rectal polyps but also had a stricture of the rectum and perhaps an anorectal abscess or a fistula.

PSEUDOPOLYPS AND POLYPS

The presence of pseudopolyps or polyps was the most frequent anorectal complication. This complication occurred in 22 (11%) of the 200 cases. Initially, at least, a polyp is a pseudopolyp or an inflamed mucosal tag. In a phase of chronic

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ulcerative colitis, sloughing of large portions of mucosa and submucosa may occur and leave large ulcers. An island of inflamed mucosa may be left in the center of a large ulcer. The island of inflamed mucosa is red and edematous, and it appears to be raised above the surface as the adjacent ulcer heals by the formation of a scar. Eventually, an adenoma or a carcinoma may develop in the inflamed tag (Fig. 1).

In cases in which this complication develops, the patients should be observed periodically and the polyps should be fulgurated at the proper time. Ideally, fulguration should be performed during a remission of the chronic ulcerative colitis. In some instances, fulguration of the polyps will cause a temporary exacerbation of the colitis. In cases in which the polyps cannot be observed with the sigmoidoscope, they should be checked periodically by means of roentgenographic examination of the colon. If such examination discloses evidence of a malignant change or an increase in the size of the polyps, ileosigmoidostomy or ileostomy and

Fig. 1.—Scarring of portion of intestinal wall which previously was denuded of mucosa. A mucosal bridge and a polypoid tag also are visible. Microscopic examination of a specimen of the polypoid tag disclosed an adenoma.

Fig. 2.—Rectal stricture slightly more than 1 cm. in diameter. The patient did not have any symptoms of obstruction and was not aware of the presence of the stricture.

colectomy should be performed. It is interesting to note that such examination may disclose considerable variation in the size of an individual polyp. This variation is dependent on the state of the colitis. A polyp which was 2 or 3 cm. in diameter on one occasion may be found to be only half that size a few weeks later. This decrease in size probably is due to a decrease in the amount of edema fluid in the polyp.

The polyps were fulgurated in 13 of the 22 cases in which this complication occurred. This operative procedure did not cause any serious untoward effect. In the remaining nine cases in which this complication occurred, fulguration was thought to be contraindicated, at least when the patients were last observed, because of the activity of the chronic ulcerative colitis or because a stricture prevented adequate exposure of the polyps.

STRICTURE

Intestinal stricture is a late complication of chronic ulcerative colitis. Stricture of the rectum was the second commonest complication in this group of cases. It occurred in 19 (9.5 %) of the 200 cases. Although generalized narrowing and

shortening of the colon are the rule rather than the exception in cases of chronic ulcerative colitis, in this paper the term "stricture" will be used to designate localized narrowing of the lumen of the intestine.

The stricture most commonly occurs in the last few centimeters of the rectum, and it results from the repeated occurrences of internal abscesses and the consequent fibrosis of the submucosa and muscularis and the narrowing of the rectal lumen. Treatment of the abscesses at the proper time will do much to prevent the formation of strictures. A stricture also may result from healing of a portion of the rectum that has been denuded of mucosa.

The mere presence of a stricture is not always an indication for ileostomy. In several of the 19 cases in which this complication occurred the stools were liquid or soft and could be passed through a very small lumen. As a result, the patients did not know that they had a rectal stricture (Fig. 2). Operation for the stricture was performed in only 2 of the 19 cases. In both of these cases, the stricture was of the diaphragmatic type and there was little if any evidence of activity of the colitis at the time of operation. When the patients in these two cases first were observed at the clinic, they were passing liquid or watery stools frequently, but the stools subsequently became semiformed and the patients had symptoms indicative of partial obstruction of the intestine. The stricture was incised. After the operation, a warm retention enema was administered daily, and the strictured portion of the rectum was dilated once a day in order to maintain an adequate lumen while healing was taking place. Rectal diathermy also may be used postoperatively in cases of this type.

ANORECTAL ABSCESSES AND FISTULAS

An anorectal abscess and fistula occurred in 15 of the 200 cases. These should be considered major complications of chronic ulcerative colitis, and the manner in which they are treated may alter the entire course of the colitis. An anorectal abscess may occur early in the course of chronic ulcerative colitis. Its presence may overshadow the colitis, and the patient may date the onset of the colitis from the abscess. When an anorectal abscess is developing, or when it is suspected that such an abscess is developing, the patient should be hospitalized and hot moist packs should be applied to the site of the abscess. Antibiotics have not proved effective in the treatment of anorectal abscesses. Incision and drainage should be performed with general anesthesia, preferably induced by the intravenous injection of thiopental (Pentothal) sodium. The incision should be larger than that used in the average case of ischiorectal abscess. The margins of the incision should be well débrided, in order that the wound may remain open and drain until a fistulectomy can be performed in a quiescent stage of the colitis.

I believe that some surgeons have been too conservative about performing a fistulectomy in cases of chronic ulcerative colitis. Although this operation may result in an indolent wound, anorectal abscesses may recur and produce rectal stricture, rectovaginal fistulas, and anal incontinence if the operation is not performed. At the clinic, it has been our practice to perform a fistulectomy while the colitis was quiescent or in a stage of remission. This operation was performed in 7 of the 15 cases in which fistula was present. In one of the cases, the patient had an anovaginal fistula. In all of the seven cases in which a fistulectomy was per-

formed the results were gratifying, and it was felt that the operation prevented a recurrence of the abscesses. Activity of the colitis precluded a fistulectomy in 8 of the 15 cases.

ANAL ULCERS AND FISSURES

Although seemingly insignificant when compared with the colitis, anal ulcers or fissures can be the most distressing complication as far as the patient is concerned. Palliative measures, such as hot moist packs, anesthetic ointments or suppositories, or hot anal irrigations, at the best, afford only temporary relief. Many anal ulcers and fissures remain chronic because of inadequate drainage. An overhanging edge of skin may prevent adequate drainage of an anal ulcer. In cases of anal fissure, a sentinal pile frequently prevents adequate drainage and causes a great deal of anal spasm. An anal fissure, a spontaneous indolent ulcer, or an ulcer resulting from a previous anal operation was present in 9 of the 200 cases. If the patient's general condition will permit excision of an overhanging edge of skin, this procedure frequently will be followed by healing of a fissure or an ulcer. This procedure produced a satisfactory result in the three cases in which it was used. Palliative treatment was used in the six remaining cases.

HEMORRHOIDS

Most patients with chronic ulcerative colitis will have a variable amount of hemorrhoidal tissue. Whether or not the hemorrhoids should be considered as a complication of chronic ulcerative colitis or vice versa is not significant. The important fact is that they coexist and that the early symptom of chronic ulcerative colitis, that is, the passage of blood, may be very similar to the early symptom of hemorrhoids. During the early phase of the colitis, that is, when it is confined to the distal part of the rectum, a hemorrhoidectomy may be performed unwittingly, with the result that the patient will continue to pass blood; an exacerbation of the colitis may occur or the anal wound may fail to heal. Some patients will date the onset of their colitis from the hemorrhoidectomy, when an early phase of the disease actually preceded the anal operation. This emphasizes the importance of examining the bowel above the anus before any anal operation is performed.

ANAL INCONTINENCE

This is certainly one of the major complications of chronic ulcerative colitis, and it may be the reason for doing an ileostomy and a colectomy. Incompetence of the anal muscles usually results from recurrent abscesses causing fibrosis, with immobilization of the muscles. Anal incontinence also may result from performing a fistulectomy followed by long-continued packing of the wound. In my opinion, many instances of anal incontinence could be prevented by performing a fistulectomy when the condition of the patient permits. An attempt to relieve the incontinence was made in only one of three cases in which this complication was present. The result of the operation was only partially satisfactory. A low-residue diet, washing out of the lower part of the bowel with an enema of plain water, and the oral administration of methylcellulose to give form to the stool may be valuable adjuncts in treating a patient in whom ileostomy or a more radical operation is contraindicated.

CARCINOMA

Carcinoma occurred in only 1 of the 200 cases in this group. Various authors have stated that this complication will develop in 2 to 5% of cases of chronic ulcerative colitis. In a recent statistical study, Bargen, Sauer, Sloan, and Gage found that cancer occurred in patients with chronic ulcerative colitis 30 times more frequently than it did in persons of similar age groups in the general population. It obviously is a major complication, and, like polyps, it most frequently occurs in the rectum or rectosigmoidal region. Once a carcinoma develops, the procedure to follow is clear-cut; ileostomy and colectomy should be performed. It is our opinion at the clinic that polyps which develop in cases of chronic ulcerative colitis have the same malignant potentiality as do other polyps and that selection of a proper time to eradicate them by fulguration will help prevent the subsequent development of carcinoma.

CONCLUSIONS

With the present knowledge, or perhaps lack of it, radical operations such as ileostomy and colectomy will continue to be lifesaving measures in many instances, but exercising good judgment in the treatment of the anorectal complications in chronic ulcerative colitis may alter the entire course of the disease and in some cases may obviate more radical operation.

During an active phase of the colitis, anorectal operations should be limited to emergency procedures, such as incision and drainage of abscesses.

During remissions of the disease, operation for anorectal fistulas is not only permissible but advisable. By this means, recurring abscesses, which may result in a rectovaginal fistula, rectal stricture, or anal incontinence, may be obviated.

Selecting the proper time to fulgurate polyps complicating chronic ulcerative colitis may be the means of preventing the development of carcinoma in some instances.

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PLASMACYTOSIS OF BONE MARROW

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IN RECENT YEARS an increased percentage of plasma cells in the bone marrow and other tissues of the body has been noted in many diseases other than the primary malignant plasmacytic diseases (multiple myeloma, diffuse plasma cell myelosis, and plasma cell leukemia). This condition has been termed plasmacytosis. Plasmacytosis may be considered of clinical importance for two reasons: 1. It requires differentiation from malignant plasmacytic disease. 2. Its diagnostic and clinical significance requires appraisal. In this study we wish to review our experiences with 50 cases of plasmacytosis of the bone marrow during the past six years.

MATERIAL AND METHODS

Between Jan. 1, 1948, and June 15, 1953, a total of 727 bone marrow examinations were performed at Parkland Hospital. Of these there were 76 preparations which showed a plasma cell count of 5% or greater. Five per cent has been arbitrarily selected as the level at or above which the percentage of plasma cells are considered abnormal, since in 500 cell counts, as herein conducted, the normal plasma cell percentage varies between 0 to 2%.[1] Thirteen of the bone marrow preparations showing an increased percentage of plasma cells were considered diagnostic of multiple myeloma (1.8% of the total). These 13 examples were obtained from five patients.

Sixty-three marrow preparations (8.7% of the total) revealed an elevated percentage of plasma cells which was considered to represent benign plasmacytosis. This opinion was based on the percentage of plasma cells, their morphologic features, clinical findings of the case, and, in some cases, the autopsy material. These 63 preparations were obtained from 50 patients. Data concerning these 50 patients are presented. Where more than one bone marrow examination was done, data concerning the preparation which contained the highest percentage of plasma cells are given.

Bone marrow was obtained generally by sternal aspiration, occasionally from the ilium or spinous process. One tenth to 0.3 cc. of bone marrow was aspirated into a dry sterile syringe; the aspirated material was placed on a glass slide; small clumps of marrow were transferred to cover glasses and cover glass smears drawn. The cover glass smears were stained with Wright's and Giemsa's stains. The smears were dried and mounted. A differential count was performed on 300 to 500 cells.

RESULTS

The Table gives the clinical diagnoses and bone marrow findings in the various cases. The highest percentage of plasma cells in the bone marrow was 21%, while 5% was arbitrarily selected as the lowest limit. These cases are arranged in order of the plasma cell percentage. Thirteen cases had a percentage greater than 10%; 13 cases, from 7 to 10%, and 24 cases, from 5 to 7%.

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Case No.	Race	Sex	Age, Yr.	Diagnosis	Bone Marrow Findings				Differential Count/100 Plasma Cells, %					
					Myeloid Elements, %	Erythroid Elements, %	Eosinophiles, %	Plasma Cells, %	Plasmablasts	Proplasmacytes	Plasmacytes	Degenerated Plasma Cells	Multinucleated Plasma Cells *	Clumps of Plasma Cells *
1	N	F	63	Myoma with uterocolic fistulae	88.2	11.8	2.2	21.5	1	7	87	5	+	+
2	N	F	57	Purulent arthritis of knee; penicillin reaction with skin rash	95.3	4.7	13.0	16.0	0	4	77	19	+	—
3	N	F	48	Pulmonary vascular sclerosis; collagen disease (?)	68.0	32.0	0	14.5	0	6	85	9	+	—
4	W	M	50	Portal cirrhosis	83.7	16.3	2.7	14.3	3	4	77	16	+	—
5	N	F	37	Disseminated lupus erythematosus	82.7	17.3	0.7	13.7	0	3	89	8	+	—
6	N	F	50	Boeck's sarcoid	89.4	10.6	2.2	12.2	0	6	87	7	—	—
7	N	F	76	Carcinoma of pancreas	59.0	41.0	2.0	12.0	Slide not available					
8	N	F	33	Aplastic anemia, cause unknown	76.25	23.75	1.0	11.5	0	9	80	11	—	+
9	N	F	19	Aplastic anemia, cause unknown	78.0	22.0	3.0	11.0	0	8	82	10	—	—
10	W	M	26	Acute aplasia of bone marrow, Mesantoin-induced	100.0	0	0	11.0	Slide not available					
11	W	M	66	Portal cirrhosis	66.1	33.9	3	11.0	0	4	81	15	+	+
12	N	M	44	Scleroderma, generalized	77.25	22.75	3.25	11.0	0	7	80	13	+	—
13	N	F	58	Meningitis, probably tuberculous	66.25	33.75	1.25	10.5	1	5	90	4	—	—
14	N	M	90	Bronchopneumonia	74.5	25.5	3.5	9.5	0	5	89	6	+	—
15	W	F	78	Metastatic carcinoma, primary site undetermined	65.4	35.5	0.5	9.5	0	7	85	8	—	+
16	N	M	15	Disseminated coccidioidomycosis	85.0	15.0	6.25	9.5	0	5	86	9	—	+
17	N	M	52	Miliary tuberculosis	60	40	0.66	9.33	0	10	74	16	—	—
18	N	F	25	Disseminated granuloma inguinale	84.75	15.25	2.0	8.75	1	6	91	2	+	+
19	N	F	19	Disseminated lupus erythematosus	81.6	18.4	3.2	8.4	4	10	81	5	+	+
20	W	M	48	Primary amyloidosis	88.3	11.7	1.3	7.7	Slide not available					
21	N	F	19	Disseminated lupus erythematosus	81.0	19.0	0	7.5	0	12	75	13	—	—
22	N	F	32	Typhoid fever; bone marrow depression, chloramphenicol-induced	88.5	11.5	5	7.5	0	5	87	8	+	+
23	N	F	58	Exfoliative dermatitis, cause unknown	77.75	22.25	11.75	7.5	0	4	88	8	+	—
24	W	M	41	Portal cirrhosis	71.5	28.5	2.5	8.25	0	2	85	10	+	—
25	N	M	44	Tuberculosis of rectum	89.0	11.0	2.0	7.0	Slide not available					
26	N	M	37	Portal cirrhosis	55.5	44.5	0.25	7.0	0	2	86	12	+	—
27	W	M	61	Bronchiectasis	70.6	29.4	12.0	6.8	0	5	83	12	+	+
28	N	F	24	Anxiety neurosis; leucocytosis, unexplained	73.75	26.25	1.5	6.75	Slide not available					

29	N	M	15	Amebiasis	81.0	19.0	0.25	6.75	0	6	89	5	+	—
30	N	F	19	Chronic osteomyelitis of femur; hematuria, unexplained	76.6	23.4	6.6	6.6	0	3	91	6	+	+
31	W	F	50	Portal cirrhosis	53.0	47.0	2.5	6.5	2	18	71	9	—	—
32	W	F	30	Diabetes mellitus; tuberculosis of cervical lymph nodes	64.5	35.5	5.25	6.25	3	12	81	4	—	—
33	W	F	38	Tuberculosis of rectum	80.0	20.0	1.0	6.0	Slide not available					
34	W	M	48	Mitral stenosis; congestive heart failure	76.0	24.0	3.0	6.0	Slide not available					
35	N	F	72	Cholelithiasis; rectal bleeding, unexplained	74.0	26.0	2.66	6.0	0	4	90	6	—	+
36	W	M	47	Pyorrhea; unexplained weight loss	45.75	54.25	0.5	6.0	0	3	90	7	—	—
37	N	F	25	Transfusion reaction with anuria	90.0	10.0	1.25	5.75	0	7	77	16	—	—
38	N	F	53	Arteriosclerotic heart disease; congestive heart failure	71.25	28.75	1.0	5.75	1	4	90	5	+	—
39	W	F	37	Portal cirrhosis	59.0	41.0	0.5	5.75	0	3	93	4	+	—
40	N	M	38	Acute rheumatic fever	93.5	6.5	1.0	5.5	0	9	77	14	+	—
41	W	M	78	Bronchopneumonia; benign gastric ulcer	86.2	13.8	4.0	5.4	0	1	96	3	+	—
42	N	F	41	Actinomycosis of jaw	61.0	39.0	9.0	5.25	0	10	84	6	—	—
43	N	F	17	Pelvic cellulitis	60.4	39.6	0.6	5.2	0	4	91	5	+	—
44	N	M	51	Pulmonary emphysema; spontaneous pneumothorax	63.0	37.0	1.5	5.0	0	0	95	15	+	—
45	N	F	68	Adenocarcinoma of uterus with metastases	64.5	35.5	0.5	5.0	Slide not available					
46	N	M	23	Sickle-cell anemia; transfusion sensitization	78.0	22.0	2.5	5.0	0	5	87	8	+	—
47	N	M	8	Cerebral palsy	96.0	4.0	1.0	5.0	Slide not available					
48	W	F	30	Acute aplasia of bone marrow, Mesantoin-induced	81.0	19.0	0	5.0	0	8	82	10	+	—
49	N	F	27	Thyrotoxicosis; iodine sensitivity	76.25	23.75	15.5	5.0	0	0	91	9	—	—
50	N	M	40	Portal cirrhosis	73.0	27.0	4.0	5.0	0	4	86	10	—	—

* +, cells present; —, cells not present.

The wide variety of clinical diagnoses demonstrated the variegated background of plasmacytosis. In some instances it was difficult to decide what factor was potentially the most important etiologically in plasmacytosis. In 10 cases (20%) a background of hypersensitivity or an antigen-antibody reaction to some agent was likely. These cases included the following: Case 2, a patient who developed a generalized erythematous rash on penicillin therapy for purulent arthritis of the knee; Cases 10 and 48, patients who developed acute aplasia of the bone marrow following 3-methyl-5,5-phenylethylhydantoin (Mesantoin) therapy; Case 22, a patient with typhoid fever who developed a pancytopenia while receiving chloramphenicol (Chloromycetin); Case 23, a patient with exfoliative dermatitis; Case 37, a patient who had a severe transfusion reaction, with acute renal failure; Case 46, a patient with sickle-cell anemia who had been sensitized to repeated transfusions; Case 49, a patient with thyrotoxicosis who developed iodine sensitivity manifested by fever and eosinophilia; Case 8, a patient with primary refractory anemia, a hypocellular marrow, and aplasia of the megakaryocytes, believed to be in the initial stage of aplastic anemia, and Case 9, a patient with primary refractory anemia and normal cellularity of the bone marrow at the time the plasmacytosis was noted but who later showed a markedly hypoplastic marrow at postmortem examination. In these last two cases a definite etiological agent causing the injury to the bone marrow was not known.

There were seven cases (14%) which could best be grouped as "collagen disease." These cases included the following: Case 1, a patient with uterine myomas and uterocolic fistulae, hyperglobulinemia, and, shown at postmortem examination, wire-loop lesions of the glomeruli of the kidneys; Case 3, a patient with pronounced hyperglobulinemia who at postmortem examination showed wire-loop lesions of the glomeruli, pulmonary vascular sclerosis, and a partially organized protein precipitate in the pulmonary vessels (neither of these patients had examinations for L. E. cells); Cases 5, 19, and 21, patients in whom L. E. cells were demonstrated and who had clinical features compatible with disseminated lupus erythematosus; Case 12, a patient with generalized scleroderma, and Case 23, a patient with acute rheumatic fever.

There were 13 cases (26%) which had chronic infections, the majority being associated with a granulomatous inflammation. There were five cases of tuberculosis: Case 13, a patient with the clinical picture of tuberculous meningitis but from whom the tubercle bacillus was not isolated; Case 17, a patient with miliary tuberculosis; Cases 25 and 33, patients with tuberculosis of the rectum, and Case 32, a patient with tuberculosis of the cervical lymph nodes. There were four cases of other granulomatous diseases: Case 16, a patient with disseminated coccidioidomycosis; Case 18, a patient with disseminated granuloma inguinale; Case 42, a patient with actinomycosis of the jaw, and Case 6, a patient with Boeck's sarcoid. The four other cases of chronic infection were Case 29, a patient with amebiasis; Case 30, a patient with chronic osteomyelitis of the femur; Case 27, a patient with bronchiectasis, and Case 43, a patient with pelvic cellulitis.

There were seven cases (14%) of portal cirrhosis, Cases 4, 11, 24, 26, 31, 39, and 50, in all of which the diagnosis was proved by liver biopsy or postmortem examination.

There were three cases (6%) of disseminated malignant disease: Case 7 had carcinoma of the pancreas; Case 15 had metastatic adenocarcinoma from an unknown primary site, and Case 45 had adenocarcinoma of the uterus and metastasis to axillary lymph nodes.

Ten cases (20%) could not be grouped. These were Case 14, an aged patient with bronchopneumonia; Case 20, a patient with primary amyloidosis; Case 28, a patient with an anxiety neurosis and an unexplained leucocytosis; Case 34, a patient with mitral stenosis and congestive heart failure; Case 35, a patient with cholelithiasis and unexplained rectal bleeding; Case 36, a patient with pyorrhea, heart disease, and unexplained weight loss; Case 38, a patient with arteriosclerotic heart disease and congestive failure; Case 41, a patient with bronchopneumonia and a benign gastric ulcer; Case 44, a patient with pulmonary emphysema, a spontaneous pneumothorax, and anemia, and Case 47, a child with cerebral palsy.

The peripheral blood studies were compatible with the primary disease present and revealed no constant trend. Serological tests for syphilis were positive in 11 patients and doubtful in 3 patients. The serum globulin was 3.5 gm. per 100 cc. or higher in 26 patients, this determination being done in 42 patients. Thus, hyperglobulinemia was encountered in 62% of the patients tested. Cryoglobulins were present in six patients. Tests for Bence-Jones protein were conducted on the urine of 13 patients; all were negative. Skeletal x-ray films revealed osteolytic lesions suggestive of multiple myeloma in only one patient, a 15-year-old boy later proved to have disseminated coccidioidomycosis. A complete skeletal series was obtained in 11 patients. Only three patients did not have bone films of some type. All of these were negative. Thirteen cases showed an increased myeloid-erythroid ratio of the bone marrow, while 14 cases showed an increased percentage of the erythroid series. Eosinophilia of the marrow of 5% or greater was present in nine patients.

A differential count was done on the plasmacytic elements in 41 cases in which slides were available for review. The terminology of classification followed the recommendations of "The Committee for Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood-Forming Organs." [2] The mature plasmacyte was by far the predominant cell, but proplasmacytes were usually found also. Plasmablasts were seen in eight patients. The highest percentage of plasmablasts was 4%, encountered in a patient with disseminated lupus erythematosus. Multinucleated plasma cells were found in 25 patients, and plasma cells were present in clumps in 11 patients.

COMMENT

Differentiation of benign plasmacytosis from malignant plasmacytic disease may be difficult. An increased percentage of plasma cells in the bone marrow, at least in levels up to 20%, can no longer be considered by itself diagnostic of multiple myeloma. The triad of plasmacytosis, hyperglobulinemia, and cryoglobulinemia is also found in benign plasmacytic proliferations. Plasmablasts and proplasmacytes may be seen in both conditions, although usually the percentage in multiple myeloma is greater. The mature plasma cells in multiple myeloma may be indistinguishable from those in normal bone marrow. The entire clinical picture must be taken into account before a decision can be made as to whether a given case belongs in the

category of multiple myeloma or benign plasmacytosis. The absence of bone lesions and the presence of a primary disease to which the plasmacytosis may be secondary are very helpful diagnostically. Here again, however, there are pitfalls, since disseminated malignant neoplasms and granulomas may be associated with both bone lesions and plasmacytosis.

Plasmacytosis has been described usually in isolated reports, in a wide variety of conditions, including serum sickness,[3] agranulocytosis and aplastic anemia,* hypersensitivity to sulfonamides,[6] collagen diseases,† rheumatic fever,[10] rheumatoid arthritis,[11] tuberculosis,[12] granuloma inguinale,[13] lymphogranuloma inguinale,[14] Boeck's sarcoid,[7] trichinosis,[15] chronic osteomyelitis,[16] acute infections including measles and roseola infantum,[12] streptococcal pharyngitis,[17] cirrhosis of the liver,[18] lymphomas and leukemia,‡ and carcinoma.[20]

The variety of recorded clinical conditions, as well as the cases herein reported, associated with plasmacytosis may be divided into five main groups as follows: (1) sensitivity to drugs or certain antigens, (2) "collagen diseases," (3) infections, predominantly chronic and frequently of granulomatous type, (4) cirrhosis of the liver, and (5) disseminated malignant neoplasms.

The experimental literature has indicated that plasmacytosis and hyperglobulinemia may be produced by the hyperimmune state.§ Considerable attention has been given to the possibility that cells of the plasmacytic type may be associated with the production of antibody globulins.|| Both in the literature and in the present series there are some cases of plasmacytosis associated either with a definite sensitivity to a chemical or with the so-called hypersensitive state. Instances of plasmacytosis in "collagen disease" and chronic infection are suspected of having a basis in hypersensitivity. Only in the groups associated with cirrhosis of the liver and disseminated malignant neoplasms is there no clear relation to hypersensitivity.

SUMMARY

Fifty cases with an elevated percentage of plasma cells in the bone marrow are presented, representing an incidence of plasmacytosis of 8.7% in routine bone marrow preparations. A wide variety of clinical diagnoses were implicated in these cases. Hyperglobulinemia was noted in 62% of 42 cases so studied. Cryoglobulinemia was observed in six patients. Bence-Jones proteinuria was not found, and skeletal x-ray films revealed no osteolytic lesions, except in one patient with disseminated coccidioidomycosis. The plasma cells were mostly of the small mature type. In most cases a major disease capable of explaining the clinical symptomatology was identified. It was considered that the plasmacytic proliferation represented a secondary response.

Plasmacytosis must be differentiated from the primary malignant plasmacytic diseases. In doing so all available diagnostic criteria must be evaluated.

* References 4 and 5.

† References 7-9.

‡ References 5 and 19.

§ References 21-23.

|| References 24-27.

Clinical and experimental observations suggest an immunologic etiology in some cases.

ADDENDUM

While this report was in preparation Klein and Block reviewed 60 cases with plasmacytosis of the bone marrow as detected by fixed tissue preparation [*Blood* **8**:1034, 1953].

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BISHYDROXYCOUMARIN (DICUMAROL) THERAPY IN MYOCARDIAL INFARCTION

Results of Bishydroxycoumarin Therapy as It Is Practiced in a Private Hospital

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FOLLOWING the animal experimentation by Solandt, Nassim, and Best * on the prevention of mural thrombi formation and extension of coronary thrombosis with the use of heparin and following the synthesis of bishydroxycoumarin (Dicumarol), many reports † appeared in the literature favoring the use of bishydroxycoumarin therapy in myocardial infarction. The routine use of bishydroxycoumarin in myocardial infarctions was advocated by Wright and associates ‡ in their report of the Committee for Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Mycardial Infarction, under the auspices of the American Heart Association. More recently however, many reports have appeared § questioning the routine use of anticoagulants in the treatment of myocardial infarction.

It was our purpose, in undertaking this study, to determine the results of anticoagulant therapy in myocardial infarction as it is carried out in a private hospital, in the daily practice of various physicians, as internists, cardiologists, and general practitioners and not by a research team. The dosage of the drug used and the prothrombin levels were adjusted by either the attending physician or the resident on his service. Hence, some kept the prothrombin levels rather low; others, moderately low, while still others did not keep them low enough. No doubt, similar situations prevail in the daily practice in many hospitals throughout the country. We felt that a practical evaluation of anticoagulant therapy in myocardial infarction could be made more truly from such a study than from a controlled research project. Since some of the internists, cardiol-

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* References 1 and 2.

† References 3-9.

‡ References 10 and 11.

§ References 12-21.

ogists, and general practitioners did not use anticoagulants at all in myocardial infarction, while others used them routinely, a fair comparison of the results in these two groups of patients can be made.

MATERIAL

The records of 300 consecutive admissions to the Mount Sinai Hospital of patients with myocardial infarction, from Jan. 1, 1950, through March, 1952, were studied. Fortuitously it turned out that 150 received anticoagulant therapy and 150 did not. The diagnosis of myocardial infarction was based on typical electrocardiographic signs and/or autopsy findings. Of the 47 who died, autopsies were performed on 23.

Of the group that received bishydroxycoumarin, there were 121 men and 29 women, with an average age of 58.7 years and an age range from 34 to 78. Of the group that did not receive

TABLE 1.—*Sex and Age Distribution*

Age, Yr.	Treated, No.		Untreated, No.	
	Men	Women	Men	Women
20-29	0	0	1	0
30-39	4	1	3	0
40-49	19	4	8	3
50-59	39	7	36	16
60-69	48	14	46	14
70-79	11	3	12	10
80 & over	0	0	1	0
Total	121	29	107	43
Average age	57.6	59.2	59.2	62.5
Total average age	58.7		60.2	

TABLE 2.—*Sex Distribution of Associated Conditions*

	Treated, No.		Untreated, No.	
	Men	Women	Men	Women
Hypertension	23	12	23	23
Anemia	44	12	45	20
Previous infarction	27	5	28	5
Diabetes	11	5	5	15

bishydroxycoumarin, there were 107 men and 43 women, with an average age of 60.2 years and an age range from 28 to 83 (Table 1). The sex distribution of associated conditions can be seen in Table 2. The two groups are apparently comparable. Thromboembolic phenomena were diagnosed only when there were unequivocal physical and/or roentgenologic findings,[7] autopsy evidence,[4] or confirmation at surgery.[2]

The determination of prothrombin time was performed according to the method of Quick,[22] using commercial thromboplastin prepared from rabbit brain. Laboratory technicians drew all daily blood samples and performed all tests in the routine hematology laboratory. Bishydroxycoumarin was used exclusively in the treated group.

RESULTS

There were a total of 13 thromboembolic complications (Table 3) in these 300 patients with myocardial infarction. Seven were in the group who did not receive bishydroxycoumarin therapy. It must be stressed here that, of those getting

bishydroxycoumarin, in only 29.33% were the prothrombin levels constantly kept under 40% of the control prothrombin activity.

There was no significant difference in the mortality rate or incidence of thromboembolic phenomena in the patients with or without hypertension (Table 4), previous myocardial infarction (Table 4), history of previous angina (Table 5), or the coexistence of diabetes mellitus (Table 5). The data were subjected to statistical analysis, using χ-square methods. Minor bleeding episodes occurred in only three patients.

TABLE 3.—*Patients with Thromboembolic Complications*

Complication	Treated, No.	Untreated, No.
Pulmonary emboli	3	5
Cerebral emboli	1	2
Peripheral thromboemboli	2	0

TABLE 4.—*Influence of Hypertension and Previous Myocardial Infarction on Mortality and Thromboembolic Complications*

	Hypertension		No Hypertension		Previous Infarction		No Previous Infarction	
	Treated, No.	Untreated, No.	Treated, No.	Untreated, No.	Treated, No.	Untreated, No.	Treated, No.	Untreated, No.
Deaths	4	10	11	22	3	11	12	21
Living	31	36	104	82	29	22	106	96
Total	35	46	115	104	32	33	118	117
Thrombo-embolism	2	4	4	3	2	2	4	5

TABLE 5.—*Influence of Previous Angina and Diabetes on Mortality and Thromboembolic Complications*

	Angina		No Angina		Diabetes		No Diabetes	
	Treated, No.	Untreated, No.	Treated, No.	Untreated, No.	Treated, No.	Untreated, No.	Treated, No.	Untreated, No.
Deaths	7	11	8	21	7	3	8	29
Living	49	54	86	64	9	17	126	101
Total	56	65	94	85	16	20	134	130
Thrombo-embolism	3	4	3	3	2	0	4	7

The data in the two groups are comparable. The presence of hypertension, previous myocardial infarction, previous angina, or diabetes mellitus did not significantly influence the mortality or the occurrence of thromboembolic phenomena in our series. The total mortality, 15.6%, is somewhat below average figures reported. The incidence of thromboembolism is lower in both series than the average reported.

The small percentage of cases kept at adequately low prothrombin levels can probably be attributed to the reluctance of some physicians to use adequate doses, to the conservative attitude of others, and to the inexperience of still others. The

unpredictability of the action of bishydroxycoumarin in some cases may have played some role. From our findings, we question the value of routine use of anticoagulant drugs in myocardial infarction.

SUMMARY AND CONCLUSIONS

The records of 300 patients with acute myocardial infarction, 150 receiving no anticoagulants, are evaluated.

There were seven thromboembolic complications in the group not receiving bishydoxycoumarin (Dicumarol) and six in the group under therapy with the anticoagulant.

There were three minor bleeding episodes.

In only 29.33% of the patients receiving bishydoxycoumarin was the prothrombin level maintained under 40% of the control prothrombin activity.

We do not believe that anticoagulant drugs should be used routinely in patients with acute myocardial infarction.

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INQUIRY INTO ROLE OF ANTIHYPERTENSIVE DRUGS

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THE TREATMENT of essential hypertension has always been disheartening. The development, however, of the newer "antihypertensive" agents has given new hope and encouragement to patients with essential hypertension and to the physician who treats them. With the advent of these agents, it seemed worth while to study the hypertensive patients in a controlled hospital practice to determine (1) the number responding to symptomatic treatment, (2) the number requiring "antihypertensive" agents, (3) the number responding to these agents after failure to respond to symptomatic treatment, and (4) the relative effectiveness of three of these agents*—the hydrogenated ergot alkaloids (Hydergin), hydralazine (Apresoline), and hexamethonium chloride (Esomid; Hexameton).

Our previous experience with the veratrum preparations led us to exclude them in this study.

MATERIAL AND METHODS

The basis of this report is a study of all hypertensive patients admitted to a general medical and surgical hospital during an 18-month period ending July, 1953. Most of these patients had hypertensive symptoms severe enough to cause them to seek medical attention. All were men. After admission to the hospital all were given a routine hypertension work-up. All were allowed hospital activity commensurate with their physical status. All were given symptomatic treatment, consisting of rest, sedation, reassurance, weight reduction if they were overweight, and, in selected cases, a low-sodium diet. In addition, associated conditions, such as congestive heart failure, were given prompt therapy. During this initial observation period, of two weeks, the blood pressure was taken four times daily, including one night reading. If, at the end of this period, a satisfactory result was noted, symptomatic therapy was continued until the blood pressure returned to normal or had stabilized above normal. Only when the elevated blood pressure became stabilized was drug therapy undertaken. In all cases in this report the blood pressure values before treatment and after treatment refer to the mean stabilized pressure.

If the blood pressure stabilized at an elevated level and definitive drug therapy was believed to be indicated, the patient was given a trial of hydrogenated ergot alkaloids, hydralazine, or oral and parenteral hexamethonium chloride, alone or in combination. Standard dosages and methods of administration were used.

* The Hexamethonium chloride used in this study was supplied by Burroughs Wellcome & Company, Inc., Tuckahoe, N. Y., as Hexameton, and by Ciba Pharmaceutical Products, Inc., Summit, N. J., as Esomid. The hydralazine was supplied by Ciba Pharmaceutical Products, Inc., as Apresoline, and the hydrogenated alkaloids of ergot was supplied by Sandoz Pharmaceuticals, Division of Sandoz Chemical Works, Inc., New York, as Hydergin.

RESULTS AND COMMENT

During the period covered by this report 126 patients with an elevated blood pressure (over 150/90) were admitted to the hospital (Table 1). Ninety-two of these received only symptomatic treatment, for the following reasons:

1. Adequate response during observation period (37 patients). At the end of the observation period the blood pressure and symptoms in this group of 37 patients were abating. Symptomatic therapy was continued, and in all there was complete relief of symptoms with return in the blood pressure to a normal level (below 160/100).

2. Cardiac, renal, or cerebral involvement of such a degree as to contraindicate the use of these drugs (39 patients). Significant heart disease was present in 31 patients. More than half had had one or more myocardial infarctions, and the hypertension was mild. Six patients had severe renal involvement, and two had severe cerebral damage. There was some overlapping of complications in this group.

3. Associated diseases (16 patients). Other major diseases, such as cancer, tertiary syphilis, hyperthyroidism, and psychoses were present in 16 patients. It did not seem advisable to attempt treatment in this group.

TABLE 1.—*Admissions for Hypertension*

		Patients, No.
Total		126
Symptomatic treatment only		92
Adequate response	37	
Cardiac contraindications to drug treatment	31	
Renal contraindications to drug treatment	6	
Cerebral contraindications to drug treatment	2	
Other contraindications to drug treatment	16	
Drug-treated patients		34

The remaining 34 (Table 2) of the original 126 patients were treated with one or more of the following drugs: hydrogenated ergot alkaloids, hydralazine, and hexamethonium chloride (Table 3). Our experience with hydrogenated ergot alkaloids was disappointing. A few of the patients given this drug did experience a lowering of blood pressure, but for the most part this was systolic only. They developed tolerance rapidly, and the medication had to be discontinued. We no longer use this drug in the treatment of hypertension.

The hypertension of nine patients responded satisfactorily to hydralazine alone. There was complete symptomatic relief in all, and all had return of blood pressure to normal. One patient in this group died suddenly while at work in his office two months after discharge from the hospital. At the time of discharge he was asymptomatic, normotensive, and on a maintenance dose of hydralazine. The hypertension of some of the patients in this group responded equally well to hexamethonium alone, but when possible we attempted to control the hypertension with hydralazine, since it seemed safer for continued home treatment.

The hypertension of three patients was controlled on orally administered hexamethonium chloride alone. These were patients in whom a satisfactory response was not obtained with hydralazine and in whom the combining of the two was not necessary. These patients had complete relief of symptoms, and the blood pressure returned

TABLE 2.—*Data on Thirty-Four Patients with Hypertension Treated with Antihypertensive Drugs*

Patient No.	Age, Yr.	Known Duration of Hypertension	Pretreatment Symptomatology (0 to ++++)	Funduscopic Classification (Keith & Wagner)	Pretreatment Blood Pressure	Posttreatment Blood Pressure	Symptomatic Relief (0 to ++++)	Most Effective Regimen	Over-All Evaluation of Therapy (0 to ++++)
1	61	.....	+++	I	180/120	130/85	++++	Oral hexamethonium and hydralazine	++++
2	37	5 yr. Sympathectomy, 1947	+++	II	180/120	120/80	++++	Oral hexamethonium and hydralazine	++++
3	29	4 yr.	++	I	170/125	130/90	++++	Hydralazine	++++
4	45	1 mo.	++	III	160/116	140/100	++++	Oral hexamethonium and hydralazine	+++
5	56	11 yr. Malignant, 1950	+++	II	190/130	150/100 Labile	++	Oral hexamethonium	++
6	41	8 yr.	++++	IV	230/165	.....	.....	.....	0, died in uremia
7	59	6 yr.	+++	III	180/120	150/100	++	Oral hexamethonium and hydralazine	++
8	37	6 yr.	++	II	210/110	.....	.....	.....	Inadequate trial
9	39	7 yr.	++	III	190/130	190/130	++++	.....	+
10	37	5 yr.	++++	II	200/140	150/90	+++	Hexamethonium	+++
11	37	8 yr. Sympathectomies, 1945-1950	+++	II	200/135	155/95	++	Oral hexamethonium and hydralazine	+++
12	63	2 yr.	+++	II	230/130	170/110	0	.....	0
13	54	3 yr.	+++	II	180/120	180/120	0	.....	0, died with CVA
14	47	7 mo.	++	II	175/110	140/100	++++	Oral hexamethonium and hydralazine	++++
15	43	8 yr. Sympathectomy, 1950	+++	II	200/130	180/110	++++	Oral hexamethonium and hydralazine	++
16	44	3 yr.	+++	II	180/120	140/110	+++	Hydralazine	0, died
17	53	.....	++++	III	190/110	220/125	0	.....	0, died
18	52	10 yr.	+++	II	180/120	135/100	++++	Hydralazine	++++
19	57	11 yr.	++++	III	240/120	200/100	+++	Hydralazine	+
20	58	10 yr.	++++	II	160/110	130/90	++++	Hydralazine	++++
21	58	1 yr.	++	II	190/120	130/90	++++	Hydralazine	+++
22	41	7 yr.	+	II	240/140	140/100	+++	Oral hexamethonium and hydralazine	++++
23	51	7 yr. Sympathectomy, 1952	++	II	220/130	140/90	++++	Hydralazine	++++
24	57	20 yr.	++	II	180/116	135/95	+++	Hydralazine	++, sudden death 2 mo. later
25	33	8 yr.	++++	IV	190/130	140/90	++++	Hexamethonium parenterally	+++, refused further therapy and died
26	60	"Years"	+++	II	180/110	150/90	++++	Hydralazine	+++
27	52	1 yr.	++++	IV	260/164	.....	.....	.....	0, died
28	62	7 yr.	++	II	180/100	160/90	++++	Hydralazine	++++
29	59	2 mo.	+++	III	200/140	160/110	+	.....	+
30	57	1 yr.	+++	IV	220/140	160/100	++++	Hydralazine	++++
31	37	10 yr.	++	II	190/130	140/100	++	Oral hexamethonium and hydralazine	+++
32	44	10 yr. Sympathectomy, 1948	++	II	180/120	150/100	++++	Oral hexamethonium and hydralazine	++++
33	45	Unknown Sympathectomy, 1948	++	II	155/115	130/90	++++	Oral hexamethonium and hydralazine	++++
34	39	5 yr.	+++	II	205/130	145/100	+++	Oral hexamethonium and hydralazine	+++

TABLE 3.—*Summary of Results of Treatment of Hypertension*

	Patients, No.
Hypertension controlled with hydralazine	9
Hypertension controlled with hexamethonium	3
Hypertension controlled with combination of hydralazine and hexamethonium	12
No therapeutic response	4
Died	5
Inadequate trial	1

to normal. The oral product was easier to administer than the parenteral one and usually gave the same results. One patient responded to the parenteral preparation when the drug was ineffectual by the oral route. This was a patient with malignant hypertension in whom the malignant phase was reversed with parenteral hexamethonium chloride. His hypertension was adequately controlled, when he refused further therapy, left the hospital, and died several weeks later at home. The patients in this group during treatment exhibited some degree of lability of the blood pressure. At times postural hypotension was sufficient to produce symptoms.

Twelve patients required a combination of hexamethonium chloride and hydralazine. These were patients in whom a satisfactory response was not obtained with either drug alone or in whom side-reactions prevented increasing dosage of either drug alone to a therapeutically effective level. All but one of these had complete relief of symptoms and return of blood pressure to normal (150/100). The one patient had pernicious vomiting when doses sufficient to lower the blood pressure to normal were administered. Smaller doses were tolerated and relieved symptoms but gave only partial blood pressure control (180/100). Theoretically, the combination of hexamethonium chloride and hydralazine should be a more rational treatment of hypertension than treatment with either drug alone.

No response was obtained in four patients, even though maximally tolerated doses were used alone and in combination. The administration of hydralazine to two patients relieved all symptoms without lowering the blood pressure. Hexamethonium chloride in the other two patients in this group produced lability of the blood pressure, with rather marked swings at times, but without any sustained average fall and without change in symptoms.

Five patients died. Four deaths followed a progressive downhill course in spite of the administration of maximally tolerated doses of all three of the preparations alone and in combination. The condition of the remaining patient was controlled by hydralazine, with an average blood pressure (140/110) and no symptoms, but he died suddenly at home, two weeks after discharge from the hospital. This patient's average blood pressure before treatment was 180/120. Hexamethonium chloride produced severe postural hypotension and had to be discontinued. Hydralazine lowered the systolic pressure more than the diastolic, and the lowered pulse pressure may have been a factor in his death. Autopsy was not performed, nor was the mode of death reported to us.

One patient had an inadequate trial, owing to his refusal to continue on treatment.

The side-effects were, for the most part, minimal and could be easily controlled. Hexamethonium chloride was not tolerated by two patients because of incapacitating postural hypotension. Two patients could not tolerate hydralazine because of headache, lightheadedness, nausea, vomiting, cardiac palpitation, and shortness of breath. This drug had to be discontinued in these four patients.

SUMMARY

One hundred twenty-six consecutive patients with hypertension admitted to a general hospital were studied, without selection, to determine the number responding to symptomatic treatment, the number requiring antihypertensive agents, the number responding to these agents, and the relative effectiveness of these agents.

Ninety-two patients (72%) were given only symptomatic therapy—37 because of adequate response, 39 because of severe complications of their salient disease, and 16 because of advanced associated disease.

Thirty-four patients (28%) were deemed acceptable for drug therapy. Nine were controlled on hydralazine (Apresoline) only, 3 on oral hexamethonium chloride only, and 12 on hexamethonium chloride and hydralazine. Four had no response, five died despite therapy, and one had an inadequate trial of therapy.

CONCLUSIONS

The majority of hypertensive patients do not need treatment with "antihypertensive" agents. Many will respond satisfactorily to symptomatic therapy. Others, with mild hypertension, need no treatment at all.

Treatment with the antihypertensive agents should be reserved for those patients whose response to symptomatic treatment is inadequate and in whom the hypertension is progressive and is producing organic changes.

Hydralazine and hexamethonium chloride, alone or in combination, are drugs that will lower blood pressure to normal levels with relief of symptoms in most patients who fail to respond to symptomatic therapy.

Patients vary in their response to each of these agents, and there is no way to predict which drug will be more efficacious in the individual patient. Many patients respond equally well to either hydralazine or hexamethonium chloride.

Patients who do not respond adequately to either drug alone usually will respond to a combination of the two.

Hexamethonium chloride, because of its ease of administration, is preferred to the parenteral preparation and in most patients gives as good a response.

Hydrogenated ergot alkaloids (Hydergin) is an inadequate drug in the treatment of essential hypertension.

PARAMYOTONIA

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PARAMYOTONIA is a congenital and inherited muscle disorder manifested by spontaneous contraction and paresis of various muscle groups upon exposure to cold. It represents the rarest of the group of muscular diseases known as myotonias, which also includes myotonia congenita, or Thomsen's disease, and myotonia dystrophica.

HISTORY AND INCIDENCE

Thomsen in 1876 [1] published his treatise on myotonia and traced the disease in his own family as far back as 1742. Erb's classic monograph appeared in 1886,[2] describing the clinical picture and basic electromyographic findings in myotonia congenita. Simultaneously with Erb's work, Eulenberg,[3] in 1886, described a family in which a form of myotonia occurred in the affected members only after exposure to cold, and he termed the condition paramyotonia. The muscle affection involved some 29 persons, traced through six generations, and by 1916 it had been traced through eight generations. The condition was manifested by tonic spasm in the orbiculares oculi and other facial muscles on exposure to cold. In the hands the tonic state was usually transitory, but occasionally a paresis remained for hours. The lower limbs were similarly affected. Apparently Eulenberg was unable to demonstrate active or mechanical myotonia, although a typical myotonic reaction to galvanic stimulation was present even at normal temperatures.

As can be seen in the Table, later authors have described families or individuals with a similar syndrome. In all cases heredity was dominant and the condition was manifest from birth or shortly thereafter. The first ten reports represent cases with absence of myotonic symptoms and signs at normal temperatures, conforming to Eulenberg's original description. The second group, of seven reports, represents cases of paramyotonia in which myotonia, along with characteristic mechanical and electrical responses, was found even at normal temperature. Certain of these cases deserve further comment.

The case of Martius and Hansemann [4] was termed myotonia congenita intermittens, but the subject developed spontaneous muscle spasm in the extremities and myotonic reactions only after exposure to cold. Actual paresis was not described. The condition was present in 11 persons, traced through four generations. It is of interest that previous generations of this same family had typical myotonia congenita. In a similar category must be placed Delprat's [5] report of Thomsen's disease occurring in a family with paramyotonia. Paramyotonia was present in 47 persons, two of whom were similarly affected from birth but who at

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the respective ages of 19 and 14 developed typical signs and symptoms of myotonia congenita. Myotonia became widespread, while extremity and neck muscles became greatly hypertrophied.

The only previous case report of paramyotonia from the American continent was that of Rich,[6] in 1894, describing a "unique form of motor paralysis due to cold" affecting some 17 members of a family in Idaho. Recently this same family has been traced through seven generations, with the trait found in 62 persons.[7] Paramyotonia in this kindred was expressed as a tonic spasm and immobility of muscles on exposure to cold. Facial muscles were most frequently affected, but paralysis of any part on prolonged exposure to cold occurred. Rich relates the experience of one patient who retired to a cold damp room after several hours of

*Summary of Reported Cases of Various Myotonias**

Author	Cases, No.	Generations, No.	Disease	Comment
Eulenberg [3] (1886)	29	6	Paramyotonia congenita	.....
Martius & Hansemann [4] (1889)	11	4	Myotonia congenita intermittens	Thomsen's disease in family
Delprat [5] (1892)	47	5	Paramyotonia	Thomsen's disease developed in 2 patients
Rich [6] (1894)	17	5†	Motor paralysis due to cold	.....
von Sölder [8] (1895)	1	0	Paramyotonia congenita	.....
Alsberg [9] (1898)	‡	..	Myotonia congenita	.....
Lewandowsky [10] (1916)	1	0	Familiare Kaltelahmung	.....
Serog [11] (1930)	9	4	Paramyotonia congenita	.....
Schott [12] (1936)	‡	..	Paramyotonia congenita	Dystrophic signs in some cases
Wawersik [13] (1947)	14	6	Paramyotonia	.....
Friis [14] (1891)	‡	..	Myotonia congenita	.....
Hlawaczek [15] (1895)	1	0	Myotonia congenita with paramyotonia	.....
Funcke [16] (1898)	1	0	Myotonia congenita with paramyotonia	.....
Hübner [17] (1917)	15	4	Atypical myotonia	Myopathic facies; one patient previously diagnosed as having Thomsen's disease
Smith [18] (1938)	‡	..	Paramyotonia congenita	.....
Koch [19] (1943)	‡	..	Paramyotonia congenita	.....
Covernton & Draper [20] (1947)	5	2	Paramyotonia	.....

* In the first 10 reports myotonia was not found at normal temperature, but it was demonstrable in the last seven both at cold and normal temperatures.
† Recently extended through 62 persons in 7 generations.
‡ Report not available.

dancing. Failing to remove her damp underclothing, she awoke in several hours to find herself completely paralyzed except for her tongue. After exposure to warmth for several hours, she recovered completely. Rich felt that this condition differed from Thomsen's disease in that the myotonic contraction was always brought on distinctly by exposure to cold and muscles in active motion were not affected, whereas in Thomsen's disease voluntary movements bring on the spasm. These observations, as will be discussed later, do not seem to be entirely true in paramyotonia and are not valid arguments for the separate identity of the two conditions.

Von Sölder's case [8] showed myotonia at normal temperatures only after quick forceful movements and repeated movements produced profound muscle spasm. Such attacks were markedly aggravated by cold weather. In Schott's series [12] dystrophic manifestations were present, several patients showing ptosis and one

showing atrophy in the forearms and hands. There was no mention of visceral manifestations of myotonia dystrophica. Several patients of Hübner's series [17] showed myopathic facies, and another patient in this family was previously diagnosed as having typical Thomsen's disease. In several of the families the patients showed marked muscular hypertrophy, as in Thomsen's disease (Von Sölder,[8] Hübner,[17] Hlawaczek,[15] Funcke,[16] and Koch [19]). The significance of these variations will be commented upon later.

REPORT OF A CASE

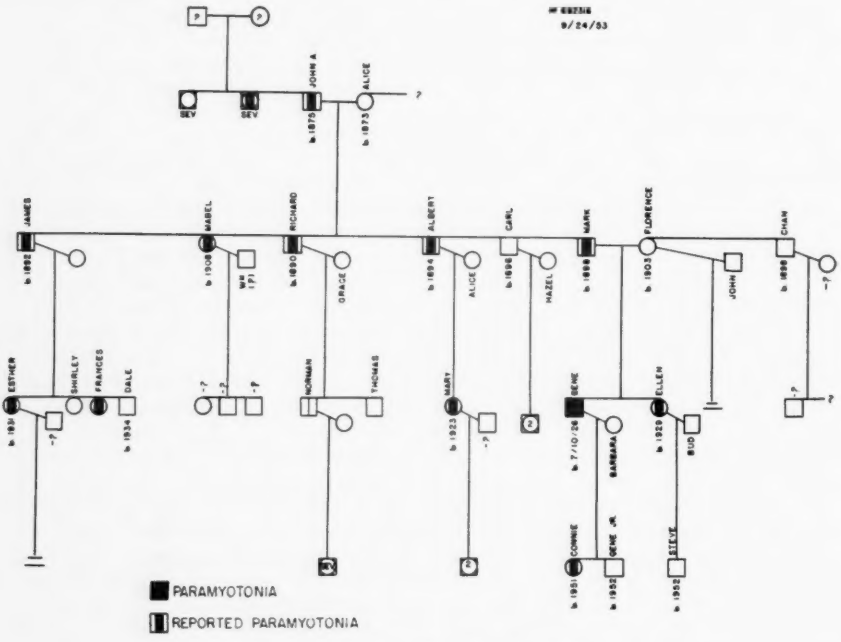
G. B. (Hosp. 692316), a 28-year-old service-station operator, was first seen in the allergy clinic of the University Hospital on Oct. 20, 1950, with the chief complaint of stiffness and loss of function of the hands upon exposure to cold. At the age of 5 years, while helping his father wash the car in cold weather, he first noticed stiffness and inability to use his hands. At that time his father told him that the "condition ran in the family." On another occasion at the age of 7 or 8 years, he developed an almost complete paralysis of the extremities on swimming in a cold lake and narrowly avoided drowning. Since then he has avoided swimming in cold water. On many occasions stiffness of the tongue and dysphagia has followed eating ice cream or drinking cold water, especially in the summertime. He specifically denied muscular symptoms at normal temperature. Although the disability may affect any part of the body exposed to cold, the hands and, more rarely, the feet are chiefly affected. Usually, after a few minutes' exposure to cold, the fingers stiffen in a semiflexed position, starting with the fourth finger of each hand, and the patient is unable to relax or straighten them. If exposure is long and severe, the entire hand becomes paretic and useless, fixed with the fingers and wrists in semiflexion. The legs may also stiffen, and movement becomes difficult, the foot becoming plantar-flexed and assuming an equinous position. On rare occasions the muscles of mastication and neck have also been affected on exposure to cold. Although difficulty in focusing the eyes has been noted, no diplopia has occurred. Upon warming, the affected part gradually regains normal function over a period of 5 to 10 minutes, but if the condition has progressed to paresis complete recovery of the part may require two to three hours in a hot bath. When the attack is severe, systemic symptoms of weakness and faintness may occur, but syncope, flushing, headache, tachycardia, or palpitation do not occur. The affected part shows no constant color change, although a slight blanching or cyanosis may appear. Pain or paresthesia is absent, although the hands may ache slightly on warming. Urticaria, edema, or swelling is not present during an attack. Continued use of the hands or repeated contractions of the fingers during exposure to cold increases the contracture and disability, with rapid progression to paresis. The degree of cold necessary to produce an attack is extremely variable and depends to some extent on the rate of change of temperature and previous degree of warmth to which the patient has become accustomed. He has learned that the more he is sheltered from cold, the more easily an attack will develop upon exposure to relatively moderate degrees of cold. For these reasons, he has more difficulty in the spring and fall, when rapid drops in temperature occur, and in midwinter, when cold is severe; however, occasional mild attacks are noted during summer on chilly evenings or when the hands are washed in cold water. With frequent repeated exposure to cold during the winter, the patient develops some tolerance after several months and actually improves slightly toward the end of winter. There was slight increase in severity to puberty, with little change since that time. Fatigue, nervousness, and debility increase susceptibility to cold.

The collateral history includes mild seasonal hay fever and bronchial asthma since the age of 5 years. Symptoms of both are aggravated by exposure to cold, but in general they have been well controlled by antihistamines and ephedrine, which have no effect on the muscular symptoms. General health otherwise has been excellent, and system review was negative.

A family history, including some 35 persons, showed an extensive history of a similar abnormality upon exposure to cold, always demonstrable within the first few years of life. The patient's sister, one of his two children, his father, three uncles, one aunt, three first cousins, and his paternal grandfather and granduncle are similarly affected, all on the paternal side of

the family (Fig.). The mother and her relatives are normal. The grandmother and a first cousin on the paternal side have asthma. None of the affected persons complain of symptoms at normal temperatures, and none has developed dystrophic symptoms or signs.

Results of a physical examination were reported as entirely normal in 1950, with the exception of nasal polyps. All extremities were of normal color and temperature. Radial, femoral, popliteal, posterior tibial, and dorsalis pedis pulses were normal and equal. There were no signs of arterial or venous insufficiency and no change in pulses with neck rotation (e. g., scalenus anticus and cervical rib maneuvers). Upon exposure to cold (10 C.) for five minutes, the fourth finger of the left hand could not be fully extended and was held in semiflexion. No marked color changes were noted. Laboratory data included a hemoglobin level of 13.9 gm., or 89%, negative urinalysis and serologic tests for syphilis, and negative test for cold agglutinins. Skin tests showed moderate to strong reactions to house and mattress dust, grasses, and fungi.



Paramyotonia in family of Patient G. B.

The patient was discharged with the diagnosis of atypical cold allergy, seasonal allergic rhinitis, and bronchial asthma and was instructed in a program consisting of daily cold baths for five minutes, beginning at 98 F. and decreasing 1 degree daily to 60 F. He was able to get down to 69 to 70 F. before symptoms occurred, but with repeated exposure he was unable to get below this without marked symptoms. Large doses of antihistamines failed to alter the attacks. Histamine hyposensitization was planned but was not carried out.

The patient was next seen on Sept. 24, 1953, because of interference with his work as a service-station operator due to inability to use his hands in cold weather. Physical examination was essentially as before, with a blood pressure of 120/65, pulse rate of 82, and respirations and temperature normal. The general musculature was well developed, without abnormal hypertrophy, and no muscle atrophy or dystrophy was noted. There was no premature baldness, cataract, or testicular atrophy. Muscle strength proved to be somewhat less than expected in comparison with the well-developed musculature. Although he had emphatically denied any

symptoms of myotonia at normal temperatures, a slight delay in relaxation of strong grip was present even at room temperature. When the hands were warmed, this became almost imperceptible. After repeated forceful movement myotonia was easily demonstrated in slowness of relaxation of hand grip and dorsiflexion of the foot. With continued repetition, paresis developed, with stiffness and spasm of the fingers in flexion and inability to relax the grip. Fine movements were less affected than gross movements. Mechanical myotonia was elicited in the deltoid, pectoralis major, gastrocnemius, and tongue muscles but not in the thenar or hypothenar groups. Although more marked after the part was cooled, the myotonic reaction to percussion was elicited at room temperature and also after warming. Immersion of either hand in ice water (8 to 10 C.) for 15 minutes produced flexion contractures of the fingers and stiffness, with inability to relax or extend them. No change in pulses, heart rate, blood pressure, or skin color was noted, and no swelling, urticaria, or constitutional symptoms occurred. A unilateral stellate block with production of a good Horner syndrome was performed. The sympathetic block failed to alter this reaction on repeat immersion of the hands. Intramuscular injection of 1 ampule of neostigmine (Prostigmin) and atropine failed to produce a myotonic contracture under normal conditions or to aggravate the reaction upon exposure to cold. Tripelannamine (Pyribenzamine) hydrochloride (100 mg.) and diphenhydramine (Benadryl) hydrochloride (50 mg.) orally failed to block the response to cold. Laboratory studies on this admission showed normal hemoglobin, hematocrit level, WBC count, and differential count, except for 8% eosinophiles. Urinalysis and a Watson test for porphyrins were negative. Total serum protein was 8.0 gm.; albumin, 5.7 gm., and globulin, 2.3 gm. per 100 cc., and serum potassium was 5.9 mEq. per liter during an attack. Thre was no difference in results of the above tests done on blood drawn from an immersed extremity as compared with that from the normal unimmersed extremity, and there was no difference in color of blood from the two.

Although quinine sulfate, 0.65 gm. orally three times daily, gave dramatic protection and improvement in symptoms after exposure to cold, it did not completely block the active myotonia demonstrable with repeated forceful movement even at room temperature; mechanical myotonia, likewise, was still present after quinine administration.

It is important to point out that there was little to suggest typical Thomsen's disease or myotonia dystrophica in this patient or in affected members of the family. Antihistamines had no effect on the abnormal reaction to cold. The absence of any of the usual local (e. g., swelling or urticaria) or reflex e. g., flushing, tachycardia, syncope, headache) systemic evidences of histamine release seems to rule out the participation of histamine in any of the responses to cold in this case. The absence of objective signs of vasomotor or sympathetic reflex discharge (e. g., color changes, swelling, pain, paresthesia, or rise in blood pressure) would seem to eliminate a role of the autonomic nervous system in the abnormal muscle response. Because of recent reports of the presence of cold-precipitable globulins in various seemingly unrelated diseases as well as in a few cases of unusual types of cold sensitivity,* cryoglobulins were qualitatively tested for in this case, but they were not found. Cold agglutinins likewise were absent, and upon exposure to cold the blood showed no sludging or abnormal change in viscosity. These results appear to eliminate any unusual physical or immunologic reactions in the blood itself. Unlike its effect in most reported cases of myotonia, neostigmine did not aggravate the symptoms in the dosage used.

COMMENT

In 1876, Thomsen described myotonia as a specific symptom.[1] It occurs in the hereditary diseases myotonia congenita, or Thomsen's disease; paramyotonia, and myotonia dystrophica. Myotonia is manifested by a prolonged contraction of

* References 22 and 23.

striated muscle following voluntary movement, so-called active myotonia. This is most frequently noted in the hands by inability to relax the grip upon shaking hands. It is accompanied by a specific mechanical response to percussion, consisting of a localized tonic contraction of muscle with delayed relaxation. If an affected muscle group is struck with a percussion hammer, a furrow or dimple will remain for several seconds. Its distribution corresponds to the muscle groups showing active myotonia, and it is particularly well demonstrated in the thenar, gastrocnemius, and deltoid muscles; the extensor muscles of the forearm, and the edge of the tongue. This response is termed mechanical myotonia. Likewise, upon electrical testing, electrical myotonia is manifested by a tonic, sluggish contraction with delayed relaxation after galvanic stimulation. This phenomenon, a specific characteristic of myotonia, was described by Erb in his classic monograph on myotonia congenita in 1886.[2] The basic defect in myotonia has been localized to the muscular part of the motor end-plate, which is apparently abnormally sensitive, reacting to voluntary nerve impulses or to electrical or mechanical stimulation by a series of action potentials producing continued contraction of muscle.[21] In Thomsen's disease, or myotonia congenita, the above myotonic phenomena occur constantly in variable degree of severity but are not infrequently aggravated by exposure to cold. Although usually widespread, myotonia in this condition may be localized in specific muscle groups, particularly facial and ocular muscles and the extremities. Repetition of movement usually affords some degree of relief of symptoms, and paresis does not occur. The myotonia is often widespread, begins in early childhood, and is transmitted as a simple dominant hereditary trait.[21] Although still a relatively rare disease, since Thomsen's original description it has been reported with increasing frequency, particularly in Europe, America, and Japan.[21]

There does not appear to be any difference between the myotonia in Thomsen's disease and that in myotonia dystrophica; however, myotonia frequently disappears with the appearance of dystrophy in the muscle.[21] Myotonia dystrophica, the commonest and severest of the myotonias, shows both muscular and visceral features. Dystrophy of the muscles chiefly affects those of the face, tongue, mastication, neck, and forearms, while the myotonia is most often localized in single symmetrical muscle groups, particularly the finger flexors. The voice develops a low nasal quality, and the characteristic myopathic facies, with drooping head, sagging mouth, and drawn expression appears. Visceral involvement is manifested by cataract (87%), testicular atrophy (86%) or menstrual disturbance (64%), frontoparietal baldness (83% males, 16% females), and mental and social deterioration.[21] The disease becomes manifest most frequently between 15 and 20 years of age and is progressive in nature, most patients dying before the sixth decade. It is transmitted as a simple dominant trait.[21]

Paramyotonia is characterized by spontaneous tonic muscle contraction in the part upon exposure to cold, presenting as marked stiffness and loss of function, which may progress to complete paresis if exposure is severe enough. Warming the part produces complete return to normal in minutes or hours. Characteristically, no symptoms are present at higher temperatures, motor function and muscular strength appearing normal. Unlike the situation in most cases of myo-

tonia congenita, repetition of movement usually increases the degree of myotonia and may produce paresis of the part even without exposure to cold. Pain, color changes, or swelling do not occur. Symptoms usually appear within the first few years of life, do not progress in severity, and are compatible with a normal life span. Marked muscular hypertrophy and the severe disturbances of muscular and visceral dystrophic involvement do not occur. Mechanical and electrical myotonic reactions are always present at lower temperatures and can nearly always be elicited if carefully searched for even at higher temperatures, when the patient is completely asymptomatic. In all cases simple dominant hereditary transmission has been found.

Although Erb [25] was of the opinion that paramyotonia was an entirely separate clinical entity, most authorities now consider paramyotonia to be a special variant of myotonia congenita.† This is borne out by the several reports of cases of typical Thomsen's disease in members of families of patients with paramyotonia ‡ and by those cases classified as paramyotonia but showing myotonic symptoms and reactions, not only after exposure to cold but also at normal temperatures.§ The myotonic symptoms of Thomsen's disease are commonly made worse on exposure to cold. The Table appears to show a rather clear gradation of severity of symptoms of myotonia, from Eulenberg's case to those which could just as easily be called Thomsen's disease with marked aggravation by cold, rather than any qualitative difference. The fact that in some of the early reports of paramyotonia characteristic active, mechanical, and electrical myotonia was not demonstrable at normal temperatures would not seem to require a separate classification for these cases. Not only is there a wide variation in temperature below which myotonic symptoms become noticeable but methods and extent of testing may not have been uniform. For example, the present case did not show myotonia of any clinical extent until after several repetitive contractions of the fingers at room temperature, thereby showing that exposure to cold was not a necessary factor in production of symptoms. Likewise, the usual positive thenar myotonic response to percussion was absent, although mechanical myotonia was elicited in several other muscle groups at normal temperature. There have also been several reports of cases of myotonia congenita in which the myotonia increases instead of decreasing as a result of repeated movements,[26] similar to the findings in the majority of reports in paramyotonia. Thus, it is felt that paramyotonia is merely a variant of myotonia congenita, or Thomsen's disease.

The relationship of paramyotonia to myotonia dystrophica is not quite so clear, in spite of two reports of apparently typical myotonia dystrophica and muscle atrophy occurring in families with paramyotonia.‖ Thomasen,[21] aften an extensive survey of the subject, feels that clinically and genetically the two diseases probably are not related, although other authors do not support this view.[26]

Paramyotonia must be differentiated from cases of physical allergy due to cold, which it superfically resembles. The dysphagia on swallowing cold liquids

† References 21, 26, 27, and 30.

‡ References 4, 5, and 17.

§ References 14-20.

‖ References 12 and 26.

and, in particular, drowning while swimming in cold water have been emphasized as manifestations of physical allergy to cold by Horton.[24] In cold allergy, however, the dysphagia is due to angioedema of the tongue and pharynx, and peripheral vascular collapse with shock due to histamine release into the systemic circulation is thought to be responsible for the reported fatal swimming cases. In paramyotonia these symptoms are both manifestations of myotonia or muscle paresis. Although the few case reports of paramyotonia available are not specific on the point, the patient under discussion in this paper gave a history suggestive of development of "tolerance" to repeated exposure to cold, although this was not verified by his failure to improve with repeated graduated-temperature baths. As is well known, this characteristic is widely utilized in the treatment of cold allergies, with good results in many cases. I have been unable to find any reports of muscle stiffness or paresis on exposure to cold in the literature on physical allergy. Likewise, the most characteristic manifestation of physical allergy to cold, urticaria or angioneurotic edema, does not occur in paramyotonia, nor do the systemic reflex phenomena ascribed to histamine release, with vasomotor changes, tachycardia, headache, or collapse, occur in paramyotonia. Finally, review of the literature on paramyotonia did not disclose a significant collateral or family history of allergy in the affected persons.

TREATMENT

Obviously, moving to a more temperate climate would be of distinct benefit to patients with paramyotonia, but this would not be practical for most. Smith[18] attempted to treat paramyotonia with paravertebral block, without success; in the present case unilateral stellate block failed to alter the response in the blocked extremity. Many drugs and hormones have been tried in treatment of myotonia, and this subject is extensively reviewed by Thomasen.[21] Both alcohol and calcium alleviate myotonia slightly. Their chief value lies in a potentiating effect upon quinine. Wolf[28] in 1936 first described the beneficial effect in severe myotonia of quinine, which has become standard treatment for the myotonic symptoms of Thomsen's disease. Quinine has been shown to act peripherally on muscle by reducing the ability of the muscle to sustain a tetanic contraction, by prolonging the refractory period. In addition, through its curare-like effect on the motor end-plate, it has been shown to reduce the tendency to repetitive discharge, characteristic of myotonic muscle.[29] Because of the development of tolerance to the drug, with gradual loss of effect after about eight days of daily administration, Thomasen[21] recommends intermittent treatment and reports good results with doses of quinine from 1.0 to 1.75 gm. per day. The effect of quinine may be potentiated with concomitant administration of calcium gluconate, if needed. In the present case of paramyotonia, quinine sulfate, 0.65 gm. orally three times daily, gave excellent protection against development of myotonic symptoms upon exposure to cold. The patient has learned that taking a "saturating dose" of 1 gm. upon arising in the morning, followed by 0.32 gm. at noon, and 0.32 gm. again in the late afternoon if exposure to cold is going to be severe or prolonged, produces maximum benefit. By omitting the drug over the week ends, loss of effect through tolerance has been avoided.

SUMMARY

A case of paramyotonia is described, and the condition is traced through four generations of the patient's family, involving some 13 persons. The relationship of paramyotonia to myotonia congenita and myotonia dystrophica and its differentiation from certain forms of physical allergy to cold is emphasized. This relatively rare and benign form of myotonia is characterized by a spontaneous stiffness and occasionally paresis of muscle upon exposure to cold. The extremities, in particular the hands, are most commonly affected; however, the facial, tongue, and pharyngeal muscles may also be involved. The loss of function may last from minutes to hours and is relieved by warming the part. There is no pain, edema, or color changes associated with the condition, and no characteristic constitutional symptoms. The basic defect appears to be an abnormal reaction of the motor end-plate to voluntary motor, mechanical, or electrical stimuli. The condition is hereditary and is transmitted as a dominant trait, becoming manifest usually within the first few years of life. Intermittent prophylactic treatment with quinine usually produces dramatic relief from symptoms.

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Treatment in Internal Medicine

MANAGEMENT OF CONGESTIVE FAILURE

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This is the first of a series of short papers on treatment of various disorders of particular interest to internists. The authors chosen for this series are entitled because of original investigations and special study to speak with some authority on the subjects which they discuss. They were asked by the Editorial Board to present their own ideas of the most acceptable plans for treatment of the condition under discussion rather than a comprehensive review of the literature. In almost every instance, however, the bibliographies accompanying the articles contain references to the recent important contributions on the subject. While there will at times be variations in opinions and emphasis from those expressed by other authorities in the given field, the Editors feel sure that each article will serve as a reliable and useful guide for the practicing physician. The series is presented to our readers with confidence and enthusiasm. P. S. R.

AIMS

FOR THE most part, management of the patient with congestive failure is an exercise in symptomatic therapy. Rarely one is rewarded by the discovery of thyrotoxicosis, thiamine deficiency, or constrictive pericarditis; specific treatment in these instances leads to brilliant results in almost every case. Valvular disease and arterial hypertension, found much more frequently as causes of failure, are being treated with increasing directness and some success. But there is no specific treatment for the vast majority of those aging subjects with congestive failure, whether or not increasing age is complicated by such processes as hypertension or coronary disease. In them, the aim at present is not to cure but to relieve symptoms and, if possible, to prolong useful and happy life.

Since this is so, it is important to consider whether management should be permitted to produce more suffering than do the symptoms against which it is directed. Not an academic matter, this is a practical point to be decided from time to time in individual patients before subjecting them to any more or less standardized treatment with all available measures but without thought. Patients with congestive failure need strong constitutions to survive the therapeutic hazards [1] to which they are so often exposed.

REDUCTION IN CIRCULATORY REQUIREMENTS

When the weakened heart is not able to pump enough blood to meet bodily needs, perhaps the first step in management is to reduce those needs by prescribing physical rest and mental relaxation. Without a specific patient before us no further details may be given, and the advice is often more easily spoken than followed in practice. Nevertheless, its importance would be difficult to exaggerate, and it seems likely that many of our current difficulties arise from the substitution of such

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measures as salt depletion for the more fundamental reduction in physical activity of persons who are antagonistic toward rest because of financial considerations and the tempo of modern life. On the other extreme, the potential precipitation of pulmonary edema or thromboembolism in heavily sedated patients flat in bed has been discussed sufficiently by others to require no further present comment. If no satisfactory chair is available, the head of the bed is raised at least 6 in. (15 cm.) by wooden blocks, so that the feet remain edematous rather than the lungs; removal of the great wheels from hospital beds increases the stability of this arrangement and further facilitates the use of a commode at the bedside. Mild laxatives are generally helpful.

Chloral hydrate or barbiturates in the evening and phenobarbital during the day are given in the smallest amounts sufficient to induce sleep and allay anxiety. Their effectiveness is often increased by a preliminary explanation of their expected action: as a placebo, even amphetamine aided the sleep of one man during the assault on Everest![2] The induction of hypothyroidism by means of radioactive iodine in a few selected cases [3] represents another method for diminishing the body's requirement for blood flow, conceivably by reducing nervous tension.

Finally, it should be recalled that patients with congestive failure are not all able to eat three ordinary meals daily. Preoccupation with salt restriction often leads to diet orders which specify the permitted sodium in milligrams but which fail to inform the housewife or dietitian that the congested, ill, weak patient really needs to be fed small amounts of easily swallowed and digested foodstuffs five or six times daily. It is not surprising that hyponatremia often appears after mercurial diuresis in subjects able to eat but a fraction of their low-sodium, large meals. For the obese patient, weight reduction by means of a low-calory diet is essential. In fact, diets low in calories are useful in reducing the metabolic rate and thus the need for cardiac output in any congested patient. Vitamin supplements are required, sometimes by injection, under these conditions of poor intake or absorption and loss of thiamine by diuresis [4] or perspiration.

IMPROVED CARDIAC EFFICIENCY

The gap between tissue needs for cardiac output, on the one hand, and myocardial ability to pump blood, on the other, may also be narrowed if cardiac efficiency is increased by digitalis or one of its glycosides. Choice of a preparation and route of its administration are governed by many factors in varying circumstances, but in the average ambulatory patient there is an increasing return to the selection of 0.1 gm. tablets of digitalis whole leaf. In the absence of medication within the previous two to three weeks, these may be given somewhat as follows to the ordinary adult.

Because a significant number of patients become toxic if given at once the full digitalizing dose of 1.2 to 1.6 gm., only half of this (0.6 to 0.8 gm.) is given initially. Four hours or more later, in the absence of toxic effects, half of the remainder (0.3 to 0.4 gm.) is given. As indicated, 0.2 gm. more may be given after another four hours, and so forth. This relatively rapid method is ordinarily rapid enough and rarely causes toxicity; frequent observation of the patient and his cardiac rate is essential. For more leisurely situations in ambulatory patients, 0.4 gm. daily for three or four days will do. In more acute, serious conditions one may add measures such as phlebotomy or oxygen or turn to intravenous injections of lanato-

side C (0.8 mg. at first, followed by 0.4 mg. once or twice at intervals of two to four hours). Once the patient is digitalized (beneficial results without toxic effects), a daily maintenance dose is sought during the following weeks and months. This, the amount needed to sustain usefulness without inducting toxicity, is usually 0.1 to 0.2 gm. of the leaf daily.

Digitoxin is alleged to be useful when gastrointestinal manifestations of toxicity limit the dose of whole leaf below effective levels. Herein lies its disadvantage in ambulatory patients seen only at intervals of weeks or months, for in them serious toxic arrhythmias may occur without the protection of nausea, vomiting, or diarrhea. Since these take the form of tachycardias as well as of bradycardia from A-V block, digitalis bodies must never be pushed merely because the heart rate seems to be escaping from control. Sometimes, with auricular tachycardia with A-V block or with bidirectional ventricular tachycardia, this is the signal to stop digitalis entirely and perhaps to give potassium chloride.*

If one prefers to use digitoxin, this may be given in milligrams as described above for digitalis leaf in grams. Because it is absorbed so completely after oral administration, oral and parenteral doses are virtually identical. Digoxin has a more transient effect and therefore sometimes fills a need in uremic and other ill patients in whom one especially fears prolonged toxicity. Digoxin may be given in an initial oral dose of 1.0 to 2.0 mg., followed as indicated by 0.5 mg. every three hours up to four times for digitalization; the maintenance dose is usually 0.25 to 0.75 mg. Special care is required to prevent the confusion of digoxin with digitoxin when the former is prescribed. Digoxin is given intravenously in the amount of 1.0 to 1.5 mg. as an initial dose, followed as indicated by 0.5 mg. for two or three injections at intervals of two or three hours. Either digoxin or, preferably, lanatoside C acts with sufficient promptness when injected intravenously that strophanthin is not necessary.

Digitalis or a substitute seems especially beneficial when congestive failure is accompanied by auricular fibrillation. Then, at least during rest, the sought ventricular slowing is gratifying. But because the rate may accelerate excessively during effort, fever, etc., much recent attention has been paid to the question of conversion to sinus rhythm by quinidine sulfate.† This drug is used, in this clinic, for (*a*) patients whose onset of congestive failure seems related to that of auricular fibrillation and who do not do well on other measures and (*b*) those with fibrillation and repeated thromboembolic episodes, as well as for those with certain other arrhythmias. When it is used in the presence of failure and auricular fibrillation, the patient is hospitalized and continues to receive digitalis but is not given anticoagulants. After a test dose for idiosyncrasy, quinidine sulfate is given orally in doses of 0.2 gm. every two hours for five times the first day. In the absence of toxicity or success, the individual dose may be increased to 0.4 gm. the next day and 0.6 gm. the next; it is often wiser to repeat a given day's schedule a day or two before increasing the amount of the drug. Three grams in one day is about as much as one should ever employ under these circumstances, for with more than that amount toxicity increases and successes are rare. Even when sinus rhythm reappears, clinical improvement seems to be less impressive than that in measurements of the

* References 5 and 6.

† References 7 and 8.

circulation.[9] A continuing ration of quinidine is usually recommended for the maintenance of reestablished sinus rhythm, but this by no means always prevents relapses and its rationale is questionable.

DIURETICS AND RELATED MEASURES

All too often the signs and symptoms of congestive failure persist in spite of digitalis and rest. At this point, the values of sodium restriction (by diet, resins, or both) and sodium and water loss (by diuretics, mechanical removal, or both) become obvious. The results of such programs extend beyond mere removal of edema to include reduction in atrial pressure and elevation of cardiac output [10] and are so spectacular that in some clinics attention to depletion of sodium ions takes precedence over digitalis and rest.[11] While granting the initial apparent time-saving and rapid improvement obtained by depletion in the majority of freshly hospitalized patients with congestive failure, most observers in this clinic prefer to delay these measures.

By less attention to electrolytes at the onset of management, patients and staff alike have more opportunity to observe the benefit of the fundamental program outlined above. Because mineral depletion may be outwardly effective when digitalis and other measure are usually not, as in such states as constrictive pericarditis, a few instances of specifically curable failure are more readily identified if diuretics are omitted at first; they are, of course, used later when needed. By waiting a bit, one may learn better the indicated degree of salt restriction; many patients tolerate much more than the 200 mg. of sodium daily, for example. The very effectiveness of the depletion principle is sometimes frightening, as when a subject is wrung dry almost overnight; next morning one may find a weak, prostrated, very ill patient with high hematocrit reading, a little fever, and perhaps signs of cerebral thrombosis.[12] Especially under these conditions, one may be tempted to institute anticoagulant therapy. Despite a few encouraging reports on anticoagulants as an addition to the management of congestive failure, careful evaluation of published data ‡ gives no valid basis for this procedure. Finally, there are few things more difficult to explain to other attendants or to the patient's anxious relatives than the abrupt turnabout from restriction of sodium to its administration by vein as a hypertonic solution after vascular collapse has occurred. It is much easier to avoid this need by proceeding more slowly.

Most of the ambulatory patients in our cardiac clinic are either unable or unwilling to achieve high degrees of sodium restriction dietetically, nor are they pushed very hard to do so. They have not found ion-exchange resins practicable, partly from reasons of palatability but primarily from financial ones. Many receive injections of a mercurial diuretic once or twice a week; they prefer to visit the clinic for these, or to have them injected by a visiting nurse at home, rather than to give themselves subcutaneous injections. They generally do not greatly prefer the latter route to the intramuscular one, and intravenous injections are given only rarely and then under special circumstances, as when other routes fail in very edematous hospitalized patients. Suppositories and oral dosage (from one to six tablets of chlormerodrin [Neohydrin] daily) forms of the mercurials have been disappointing in all but a very few patients. Enteric-coated tablets (0.5 gm.) of ammonium chloride,

‡ References 13 and 14.

given in amounts of 6 to 9 gm. for only a-day or two prior to injection, sometimes restore diuresis to mercury when the patient had become hypochloremic and unresponsive.§ In a very few refractory subjects with the usual nocturia and oliguria by day it has seemed that mercurial injections were more effective in the evening than in the morning.

Oral administration of carbonic anhydrase inhibitor (Diamox), a 250 mg. tablet every morning, has thus far been less than impressive, and observations reveal no effect at all from aminophylline orally, although that material often produces diuresis and other beneficial results [17] when given by injection or, more usefully, by rectal suppository. On the other hand, theophylline and sodium acetate (0.2 gm. tablet or capsule with each of three meals, one day weekly) is a potent diuretic when it does not cause gastrointestinal symptoms; theoretically, the xanthines should be particularly useful in the presence of hyponatremia, for it has been claimed that they act more upon water than upon mineral excretion.[18]

Patients in this clinic have not had good results from the forced-fluid regimen and are allowed to take fluid as dictated by thirst. Unrestricted water intake in the face of sharply curtailed intake of sodium salts, however, sets the stage for hyponatremia. This may be especially striking within hours or a day or two after the removal of large amounts of body fluids via Southey-Leech tubes or by abdominal paracentesis, whereupon vascular collapse with oliguria, retention of urea and potassium, and death may occur.‖

OTHER CONSIDERATIONS

Some miscellaneous points remain to be mentioned. In the presence of profound anemia, for example, phlebotomy is, of course, contraindicated; a transfusion of whole blood or red blood cell mass may need to be given slowly. With advanced renal failure, diuretics are generally without value or even harmful; ion-exchange resins or ammonium chloride should not be used in the presence of renal acidosis.

Chronic cor pulmonale presents a situation in which the use of morphine may cause death by respiratory arrest and in which the administration of 100% oxygen sometimes produces coma or even death with retention of carbon dioxide.[21] In congestive failure generally, the antidiuretic properties of morphine have not seemed harmful enough to counteract its great utility in allaying apprehension. Also in general, the use of oxygen in tents leaves much to be desired from the standpoint of increased oxygen concentration unless the rate of flow is increased above customary levels of 6 to 8 liters per minute or unless actual determinations are made occasionally; when well used, the tent is sometimes preferable to nasal or oronasal methods, but the simplest and most commonly used route of administration is via nasal catheter.

Quite apart from their obvious or obscure toxic effects,¶ digitalis and its glycosides are by no means effective in every patient with congestive failure, especially when sinus rhythm is present. With sinus rhythm, poor results should not be too surprising in rheumatic fever and other forms of myocarditis, acute thiamine deficiency, chronic cor pulmonale, and pure mitral stenosis. Deleterious results, no

§ References 15 and 16.

‖ References 19 and 20.

¶ References 22 and 23.

effect at all, and benefit have been observed in individual patients with each of these states,# while improvement has been observed occasionally even in the presence of chronic constrictive pericarditis.[29]

In any of the arrhythmias (not present as a toxic manifestation of the drug) with rapid ventricular rate and congestive failure, digitalis may be used and is the drug of choice[30] in all but paroxysmal ventricular tachycardia. For the latter, quinidine sulfate is preferred; it is given orally much as described above, but in more serious situations the dose is often increased in increments of 0.2 gm. every two hours if electrocardiographic control is available.[7] Quinidine sulfate is used in this way as a second choice for other arrhythmias as well, but during such therapy digitalis should usually be continued in the presence of congestion or with arrhythmias (such as auricular flutter) in which the rate of the auricles exceeds that of the ventricles. For grave situations with paroxysmal ventricular tachycardia, procaine amide hydrochloride is injected intravenously, up to 1 gm. over a 10-minute period, with electrocardiographic control. When congestive failure complicates recent myocardial infarction or occurs together with A-V block, digitalis may be used safely if given with more than the usual caution.

The refractory state of congestive failure usually represents an end-stage of dissolution, by definition failing to respond to all measures. Sometimes, however, this appears because of overtreatment rather than in spite of undertreatment; at least temporary improvement may then follow the abandonment of everything (bed rest, digitalis, sodium restriction, heavy sedation, mercurial diuretics and ammonium chloride, etc.) but sympathetic nursing and common sense.

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Progress in Internal Medicine

RECENT ADVANCES IN NUTRITION AND METABOLISM

I. Review of the Literature on General Nutrition and Protein and Mineral Metabolism, 1952

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NUTRITIONAL investigation during the past year has uncovered many findings of interest to the practicing physician. Medical aspects of nutrition have received increasing attention, as is exemplified by studies of obesity, of the therapeutic usefulness of low-salt diets, and of the role of nutrition in changes associated with the aging process. Research on many of the basic aspects of protein metabolism has been continued.

The presence of food surpluses in some areas of the world [1] and of food shortages in others poses problems of socioeconomic and political as well as of nutritional importance. Discussions of the Food and Agriculture Organizations of the United Nations relative to this and to other problems of food distribution and utilization have been described by Akyroyd.[2]

MEASUREMENT OF BODY COMPOSITION

The assessment of the nutritional status of an individual or of a population group has always been on somewhat tenuous grounds because of the lack of specific methods of measurement. Recently, new work has been undertaken using accurate and statistically valid measurements for the study of growth, development, and nutritional status (nutriture). The general use of measurement, statistics, and controls in medicine, including nutrition, has been extensively discussed in a symposium in the *British Medical Bulletin*.* Methods have been developed for studying the "lean body mass," the various fluid components of the body (plasma volume, extracellular fluid, and total body water), and the quantity of fat, both total fat and that in adipose tissue, excluding the normal intracellular fat. The methods for measuring body fluid (involving dilution of isotopic or other measurable substances) have been described by several workers † and reviewed by Robinson and McCance.[12] Discrepancies between the different methods of measuring total body water have been found in edematous patients, presumably due to differences in rates of diffusion of these substances into the edema fluid.

For the measurement of fat (and "lean body mass"), methods have been used which include direct analysis of bodies,‡ body photographs, x-ray of soft tissues, specific gravity, dilution of fat-soluble substances,[13] and the measurement of total body water. These methods give somewhat different values, the discrepancies

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* References 3-5.

† References 6-11.

‡ References 6-11.

depending in some cases upon the method and in others upon the definition of lean body mass. For example, quite different results are obtained if the fat in the parenchymal cells is considered a part of lean body mass rather than included with fat depots. This and other problems remain to be worked out.

NUTRITION, AGING, AND CHRONIC DISEASE

The separation of the process of senescence from the chronic diseases which so often occur in old age, such as diabetes, diseases of the heart and arteries, cancer, and the arthritides, is indeed difficult and has attracted some attention.§ It is now common knowledge that many of these "degenerative diseases" are related to disturbances of nutrition, and, in fact, they may be prevented in some instances and treated in others by special nutritional means. To what extent senescence itself may be altered or its onset delayed by careful attention to nutrition is quite unknown, but the problem is being attacked.

As one would expect, there is a definite increase in fat content of the body with age. This is particularly noticeable in women. The increase in fat is not simply additive but is associated with a decline in muscle mass. This was true of a group of middle-aged white-collar workers studied by Brozek.[16] Two groups of these persons were selected. Those in the first group were accustomed to regular physical exercise, whereas the others had always led a more sedentary existence. They were matched for age and height. It was found that the active persons were heavier than those of the sedentary group, but the excess weight was due to an increase in lean body mass and not to fat. This suggests that the decline in lean body mass with advancing years is to some extent "disuse atrophy." Some hope is thus offered for the prevention of the loss of muscle tissue in the aged.

A number of recent books concerned with aging have appeared. The new edition of Cowdry's "Problems of Aging" contains excellent chapters on the diverse aspects of the problem.[17] Among the chapters are several of nutritional interest: McCay, "Chemical Aspects of Aging and the Effect of Diet upon Aging"; Dempsey, "Hemostatic and Histochemical Aspects of Endocrine Glands," and Shock, "Aging of Homeostatic Mechanisms." A clear discussion of the fundamental changes in cells with age is contained in the book by Andrew.[18] Statistical material with respect to aging and discussion of the public health aspects of this problem are contained in two publications from the Federal Security Agency (now the Department of Health, Education, and Welfare); one a report from the First National Conference On Aging[19] and one from the Second International Gerontological Congress.[20] An excellent study of nearly 8,000 persons over 61 years of age has been published by Monroe,[21] which emphasizes medical complications, including nutritional disturbances. Stieglitz, Portis, and King || examined 133 persons between the ages of 60 and 83, with particular respect to nutrition and the gastrointestinal tract. Included in their studies were not only the usual history and physical examination but also hematologic studies, gastric analysis, dextrose-tolerance tests, electrocardiograms, basal metabolic rates, and roentgen examinations of the gastrointestinal tract. A discussion of the psychological aspects of aging and the treatment, including the diet therapy, psychotherapy, and general medical management is given. The diffi-

§ References 14 and 15.

|| References 22 and 23.

culty in making diagnosis in older persons on the basis of history is stressed by these authors. In the older age group Rafsky and co-workers [24] found by electrophoretic analysis relatively less albumin and more globulin (beta) than in younger persons.

In view of the fact that a number of chronic diseases, especially rheumatoid arthritis, are accompanied by disturbances of collagen formation and repair, it is not surprising that considerable study has been given to the metabolism of this important and widespread protein. Of considerable interest, therefore, are studies of the rate of collagen turnover, using radioisotopes, for example, to label aminoacetic acid (glycine), an amino acid present in high concentration in collagen.¶ The results indicate that the turnover of collagen in adult animals (rats and guinea pigs) is quite slow but that it is more rapid in growing animals. Scurvy in guinea pigs or the induction of what were considered evidences of scurvy in rats on diets deficient in both vitamins A and C did not show as close a relation of vitamin C nutrition to collagen formation as would be expected from the fact that animals and man in the scorbutic state are unable to heal wounds properly, presumably by a failure to lay down collagen.[27]

Lemon, Chasen, and Looney [28] studied the blood aminoacetic acid content after the administration of benzoic acid in normal persons and patients suffering from rheumatoid arthritis. It was concluded that following sodium benzoate administration patients with rheumatoid arthritis were not able to maintain a normal serum aminoacetic acid level as well as normal persons.

NUTRITION IN LIVER DISEASE

Last year's review covered the subject of liver disease rather thoroughly, and so only certain aspects will be discussed briefly. Emphasis has been placed on the provision of an adequate diet in the treatment of most forms of liver disease, but more food may be necessary for patients with hepatitis. A large and carefully planned study among American military personnel in Japan was conducted to evaluate the usefulness of high-protein diets in the treatment of viral hepatitis.[29] Only preliminary results have been reported so far, which suggest that forcing patients to eat a minimum of 150 gm. of protein and 300 calories induced a slight (seven-day), but significant, decrease in convalescence time.

Considerable interest has been evidenced in the etiology of liver coma with the finding of an increased urinary excretion of glutamine [30] and sometimes an elevated blood ammonia concentration [31] in this condition. Moreover, impending liver coma can be induced by the administration of such substances as ammonium chloride, diammonium citrate, urea, and even increases in dietary protein in some patients.[32] This makes it necessary that care be exercised in the administration of these substances as diuretics or in providing large quantities of protein to patients with severe liver disease.

Extension of the studies of Cayer and Cornatzer [33] discussed in the previous review confirmed the marked decrease in phospholipid turnover in patients with fatty cirrhosis tested with choline or methionine administration after treatment with a 3,500 calorie, 120 to 140 gm. protein diet with choline and methionine supplements. In general, liver biopsy showed a decrease in fat content with this therapy, although there were exceptions.

¶ References 25 and 26.

Kwashiorkor. — This disease, sometimes called malignant malnutrition, is believed to be widespread in the tropical world and in many subtropical and even nontropical areas where protein nutrition is severely restricted. A survey of the disease, principally in Africa, was made by Brock and Autret,[34] acting in behalf of the Joint Expert Committee on Nutrition of the Food and Agriculture Organization of the United Nations and the World Health Organization. They suggest that this disease is a form of protein malnutrition. The children affected characteristically have been given only small quantities of poor quality vegetable protein to eat. Deficiency of amino acids (specifically methionine) and of the other factors commonly associated with high quality (animal) protein are considered important in the pathogenesis of this interesting condition. It is characterized by retarded growth, "dispigmentation" of the skin and hair, edema, and a fatty cirrhosis of the liver. The remarkable therapeutic value of dried non-fat milk solids is made clear by Brock and Autret, but, with a disease so widespread, sufficient quantities are not available for treatment, to say nothing of prevention. Changes in agricultural practices commonly used in many parts of the world are necessary from those in which foods yielding high energy but poor in protein are grown to those which yield adequate protein as well. For example, peanuts, soy beans, and certain grains could be planted rather than the high-calorie, low-protein root, cassava. The matter of preventing this disease is one of education in agricultural methods and food habits more than it is a strictly medical problem.

OBESITY

The increasing interest in overnutrition as a form of malnutrition has brought with it a number of interesting studies. Dublin and Marks [35] have investigated a group of persons issued life insurance in the years between 1925 and 1934. Somewhat more than 50,000 persons issued policies during these years and overweight at the time, but otherwise presumably well, were followed until 1950. There were about equal numbers of men and women. During the years in which the study was carried out some 6,400 died, of whom approximately 3,700 were men. Of the men the mortality was one and one-half times that expected for the general population and was higher in the younger than in the older obese persons. The women also had about one and one-half times the expected mortality, but differences with respect to age were not conspicuous. In general, both men and women had a marked increase in mortality with increasing obesity. As might be expected, the increase in mortality was due largely to cardiovascular and renal diseases and to diabetes.

Further study by Dublin and his associates [36] provides some evidence that for obese persons weight reduction is accompanied by a reduction in mortality. The important role of the physician in initiating and maintaining weight reduction and the problem of "weight reducing fads and frauds" were emphasized.

The clinical association of cardiovascular disease with obesity led to the study by Taylor, Brozek, and Keys,[37] who sought to determine whether cardiac output is increased in proportion to the increased oxygen consumption required by the metabolically active and respiring fat in the obese person. Were the cardiac output not to rise in proportion to the excess fat, an increased ability to remove oxygen from the blood would be necessary, and increased arteriovenous oxygen difference would be expected. This was the case. In fact, the increased oxygen demand in the obese

person was not supplied by increased cardiac work but by better oxygen removal. Thus, in obesity, increased cardiac work was not required for the metabolism of the additional tissue. These results do not contradict the presumed increase over normal in cardiac work required by the obese person during exercise.

Meiklejohn,[38] in discussing diet and obesity, believes that "there is undoubtedly an endogenous or metabolic cause of obesity as well as an exogenous one of simple overeating." In succinct words, he discusses the problem of a mechanism of storing energy as fat in the obese person. He believes that normal persons may have a method of disposing of excess calories which is impaired in the obese patient. Obesity, he emphasizes, is still unquestionably due to a greater food intake than can be expended by that particular person.

The problem of appetite and its relation to obesity has been approached by Mayer and his colleagues.# They have proposed a "glucostatic theory" of the regulation of food intake, which depends upon the degree of arteriovenous glucose difference. In essence, appetite is thought to be associated with a small arteriovenous glucose difference and anorexia with a greater one. In one of their studies [41] 12 obese and 12 control women were studied with respect to glucose tolerance after the ingestion of an ordinary meal and after glucose by mouth. Strikingly different curves were obtained, the obese persons having a considerably greater tolerance both to carbohydrate from the meal and to glucose. That is, there was less of a rise in blood sugar in the obese persons than in the nonobese. When dextrose was administered intravenously, a similarly increased tolerance was observed in the obese persons. The increased carbohydrate tolerance in these persons presumably leads to a more rapid disappearance of the arteriovenous difference seen after glucose ingestion. This disappearance of the arteriovenous difference has been termed by Mayer and his colleagues "metabolic hypoglycemia" and in itself is thought to lead to hunger. "Active" obese persons tend to have a period of metabolic hypoglycemia sooner than persons who maintain a normal weight, that is, "satiety is more transient."

Finally, these workers were able to show that arteriovenous glucose difference correlated closely with appetite and food intake.[42] It was found that an arteriovenous glucose difference of 15 mg. per 100 cc. or greater was never associated with hunger, whereas values approaching zero "were invariably associated with hunger." The results collected and interpreted by these workers form an important approach to the study and treatment of obesity in man.

A strain of mice with hereditary obesity has been studied by Mayer and his colleagues.* Genetic analysis indicated a recessive character for this condition. These animals were found to have a hyperglycemia which was refractory to insulin, and they consumed more calories than did their normal relations. Fasting rapidly reduced the blood sugar to normal. It was considered by Mayer and co-workers that the hyperglycemia and obesity were due, at least in part, to an altered acetate metabolism.[45] Acetate administered to the obese animals was oxidized more slowly than by the normal controls and appeared rather to be synthesized into body fat.

Mayer and his colleagues † and Pennington ‡ both agree that in obesity there is a dynamic and a static phase. The former is characterized by continued gain in

References 39 and 40.
* References 43 and 44.
† References 39 and 40.
‡ References 46 and 47.

weight, and the latter, by obesity which remains unchanged. Pennington believes that obesity is "a compensatory hypertrophy of the adipose tissues," due to a defect in pyruvate metabolism. He does agree that psychic stress may, by operating through the hypothalamus, lead to overweight, much as injury to certain areas of the hypothalamus in animals will cause hyperphagia and marked gain in weight. The group discussion approach in the treatment of obesity has been suggested by Bayles.[48] Considering the magnitude of the problem, the suggestion seems a good one. Bayles' results, however, are still too few to evaluate. An excellent brief discussion of the psychology of overeating is provided by Brosin,[49] who emphasizes that the physician treating an obese patient must understand the emotional conflicts and altered interpersonal relations before adequate therapy can be given.

PROTEIN AND AMINO ACIDS

In an excellent review of the nutritive evaluation of protein, Mitchell [50] concluded that, although chemical analysis of the amino acid composition of proteins would give a "first approximation of their value in metabolism," true nutritive value depends finally upon biologic evaluation. The importance of not "relegating a food to an inferior class because its proteins are not of high biologic value" was stressed by Hart.[51] He also pointed out the nutritional value of a mixed diet for those whose diet habitually contains proteins of low biological value. In this way, an amino acid deficiency in the proteins of one food is replaced from another food, not deficient. This concept is of great importance in many countries of the world, where foods low in protein and deficient in certain amino acids comprise most of the daily diet (*v.s.* under discussion of kwashiorkor). The "poor rice diet" of South India has been studied in rats by Devadas and Sutton,[52] who found an unidentified growth-promoting factor in egg yolk when it was added to the rice diet. Moreover, in India and many other parts of the world, mixtures of cereals have been shown to enhance greatly the biological value of the proteins in the diet by supplying more nearly optimal quantities of the essential amino acids.

The effect of growth hormone on nitrogen metabolism was studied by Bartlett and Gaebler.[53] The administration of growth hormone was found to lead to nitrogen storage and an increase in the plasma proteins, especially albumin and certain of the globulins. Although the disturbances in carbohydrate metabolism in diabetes and in Cushing's disease are quite different—for example, insulin is specific in diabetes but insulin-resistance is characteristic of Cushing's syndrome—both conditions in their uncontrolled state are usually characterized by protein loss, negative nitrogen balance, and protein undernutrition. Studies by Forker and Chaikoff [54] have demonstrated that the protein metabolism in induced diabetes in dogs is an antianabolism rather than an increase in protein catabolism. The same seems to hold true for Cushing's syndrome in man, as originally proposed by Albright [55] and largely substantiated by Parson, Krispell, and Ebbert.[56]

Amino Acids.—Two new amino acids have been described. One, reported by Wooley, Pringle, and Braun,[57] was isolated from the toxin of Pseudomonas tabaci, and the other was found after the hydrolysis of the diphtheria bacillus and from tubercle bacilli by Asselineau, Choucrown, and Lederer [58] and by Work.[59] Both are structural analogues of methionine and may have an action as antimetabolites.

Oesterling and Rose [60] studied the tryptophan requirement for growth of young white rats with particular reference to the relationship between tryptophan and nicotinic acid (niacin) metabolism. They demonstrated that nicotinic acid exerted an added effect on growth when limiting qualities of tryptophan were given in addition to a purified diet. However, when the minimum requirement for tryptophan was reached, additional quantities of nicotinic acid did not stimulate growth.

Imbalance among amino acids in the diet has received considerable attention, and it is known that when a minimal quantity of one or more amino acids is fed growth stops and nitrogen balance becomes negative. This is also true in the relationship between certain amino acids and vitamins, as noted above for tryptophan and nicotinic acid.[61] A puzzling relationship of threonine to tryptophan utilization has been found.[62] Feeding the amino acid threonine appears to interfere with the utilization of tryptophan. No positive explanation for this amino acid antagonism has been found, although it has been suggested that threonine may interfere with the process of manufacture of enzymes in the gastrointestinal tract.

The so-called nonessential amino acids have been known to lead to improved growth in animals when added to a diet composed exclusively of the essential amino acids. Further work emphasizing the relative nature of the nonessentiality of certain amino acids has been presented by Rose, Burr, and Sallach,[63] who studied the effect of the omission of several nonessential amino acids in the diet. Although all of the nonessential amino acids could be manufactured to some degree with this form of dietary restriction, limitation of growth did occur, presumably owing to failure of the organism to manufacture a sufficient amount of one or more of these amino acids, even though some synthesis continued.

Microbiological determination of the plasma concentrations of the eight amino acids essential for man and of histidine and arginine in surgical patients in various states of nutrition were studied by Everson and Fritchel.[64] A decrease in plasma amino acids was found in a poorly nourished group, including each of the individual amino acids except for arginine. The previously well-nourished patients did not exhibit a true difference between the total of the 10 amino acids determined and that found in normal persons. The authors related the hypoaminoacidemia to malnutrition rather than to the particular surgical condition from which each of the patients was suffering. Further studies demonstrated that immediately following surgical operation there was a fall of the plasma amino acid level (total of the 10 amino acids), which, however, rose to normal by the morning of the first postoperative day and remained normal on the third and seventh days. No increase in the urinary excretion of the individual amino acids was observed to be of sufficient degree to account for lowering the plasma levels of the amino acids.

In this connection, Sebrell and McDaniel [65] studied the requirements for individual amino acids following hemorrhage in rats on controlled diets. Although certain of the amino acids seemed more necessary than the others for blood regeneration (for example, histidine for hemoglobin regeneration, as might be expected from the high concentration of this amino acid in the hemoglobin molecule), omission of each of the amino acids had some deleterious effect upon the regeneration of the hemoglobin, red blood cells, white blood cells, or serum proteins.

SODIUM AND POTASSIUM

Restriction of sodium intake, chiefly by reduction in dietary sodium, has been increasingly popular for the treatment of congestive cardiac failure, hypertension, ascites and edema formation in cirrhosis of the liver, and in the toxemias of pregnancy. Several reasons can be given to account for the current widespread use of sodium restriction. First, a number of studies have demonstrated that sodium restriction is highly effective in controlling edema formation, with or without ascites, in congestive heart failure, in cirrhosis of the liver,[66] and sometimes in renal disease. The effectiveness of sodium restriction in the treatment of hypertension has been variable, with excellent results obtained by Kempner [67] and his colleagues with the "rice diet" but less consistently good results arising from other clinics.[68] Secondly, the advent of flame photometry as a relatively simple and rapid method for determining sodium and potassium has made the analysis for these elements in blood, urine, and foods far easier than before. Finally, better knowledge of the sodium content of foods and the ready availability of foods processed without added sodium chloride or with sodium actually removed during processing have made sodium-restricted diets much more easily prepared and more rigidly restricted in sodium than before. Several reports of analyses of the sodium content of foods, both natural and packed,§ and a number of books || describing sodium-restricted diets and providing recipes have been published. The Council on Foods and Nutrition of the American Medical Association is now accepting certain special-purpose foods especially prepared for use in sodium-restricted diets.[77] The acceptance of these foods by the Council at once makes available to physicians and patients foods processed for this special purpose for which accurate and reliable figures of the sodium content appear on the label (in milligrams of sodium per 100 gm. of product).

These foods fall into several classes: (1) foods naturally low in sodium content; (2) foods naturally low in sodium but to which sodium in one form or another is usually added during processing but is omitted for this special purpose; (3) foods not necessarily low in sodium but necessary for a well-rounded diet, specially packed so that the sodium content is known; (4) foods naturally containing significant quantities of sodium but from which much has been removed by processing to make them suitable for a rigidly sodium-restricted regimen.

The restriction of sodium intake, although of definite therapeutic value in certain diseases, is not without its harmful effects and even dangers. Prolonged sodium restriction apparently does no harm if the renal and sweat mechanisms which normally maximally conserve sodium in this circumstance are intact. Many persons with congestive heart failure and, particularly, some patients with chronic nephritis have a greatly reduced effectiveness of the renal mechanism for salt retention, so that sodium continues to be excreted in the urine (and sweat) even when the intake in food is reduced to a very low level.[78] The same situation may be induced in certain patients by the repeated administration of mercurial diuretics, particularly when the sodium intake is greatly restricted.[79] These circumstances lead to a body depletion of sodium which makes itself known by oliguria, continued or increased edema formation, extrarenal azotemia, cramps in the extremities, and even a fatal outcome.

§ References 69-71.

|| References 72-76.

This syndrome in its acute stages can be readily treated by the intravenous administration of hypertonic saline solution and by restriction of water intake. When the state of sodium depletion is chronic, however, it may be more difficult to recognize but still may play an important part of the genesis of weakness and general debility in certain patients. It should be emphasized again, however, that most patients have normal homeostatic mechanisms and are able to manage well even severe sodium restriction and benefit by the associated control of edema and ascites formation.

Varying degrees of sodium retention from the administration of cortisone and adrenocorticotropic hormones is observed and is to be expected. Here again, dietary restriction of sodium will decrease or even prevent edema formation and may reduce in severity some of the other toxic manifestations from the chronic administration of these drugs.[80]

Suggestive evidence is available that at least one of the factors in the genesis of retrolental fibroplasia of premature infants may be the sodium content of the formula. Hepner and Krause [81] found some epidemiological evidence that use of formulas high in sodium chloride rather than the relatively low-sodium-containing breast milk led to a higher incidence of this unfortunate condition. There certainly are other etiological factors, for the disease is known to occur also in infants fed breast milk alone, which is relatively low in sodium chloride compared to many formulas. The possible relationship of sodium intake to this disease awaits further investigation and substantiation.

The relationship of blood concentrations of sodium and potassium to paralytic ileus has been studied by Streeten and Williams [82] in dogs. Depletion of sodium chloride led to a gradual decrease in intestinal propulsion, which was followed by complete paralysis and which could be reversed with the injection of sodium chloride solutions. Hyponatremia and hyperkalemia accompanied the sodium depletion. Potassium administration likewise decreased intestinal motility but not to the extent that sodium depletion did.

FLUORINE

Interest in fluorine centers chiefly around its use in the prevention of dental caries, following the observation that water supplies containing large amounts of fluoride are related to mottled tooth enamel and that dental caries reaches its highest incidence where the water supply is deficient in fluorides. It was soon found that water supplies containing approximately 1 part of fluorine per 1,000,000 parts of water are associated with a decrease in dental caries. This led to the working hypothesis that the fluoride content of the water was responsible. Recently an experiment was designed involving two cities (Newburgh and Kingston), both on the Hudson River and both with a water supply low in fluoride content.¶ To one of these cities sodium fluoride was added to the water supply, beginning in 1945, while the other remained as a control. Periodic examinations were made to determine the incidence of dental caries. Some 6,200 children were studied between the ages of 6 and 12 years, about half in each of the cities. In general, a significant decrease in the incidence of caries was noted among the children drinking the fluoride-containing water. Younger children seemed to have the best results. A study in which

¶ References 83 and 84.

Colorado Springs and Boulder, Colo., were compared,[85] the former having water with a high fluoride content and the latter a low-fluoride water, has indicated that the decrease in dental caries from fluoride occurred not only in children but in adults who have lived in the area during their childhood. These and a number of other studies strongly support the evidence that fluoride added to the water supply of communities with low-fluoride water materially reduces the incidence of dental caries in children and also in adults.

Fluoride is known to exert a toxic effect when the dose is too large. Mottled enamel, mentioned above, the commonest form of toxicity, occurs at levels of fluoride in water not far above those recommended for use. It is probably harmless apart from this cosmetic effect. Higher degrees of fluoride toxicity in animals include osteosclerosis and other bone changes. The studies in the two cities of Newburgh and Kingston are continuing and will help to answer the problem of possible although highly unlikely chronic toxicity, since careful histories, physical examinations, and bone x-rays of the persons studied are being carried out. At the last report there is no evidence of toxicity.

Little is known of the storage and excretion of fluoride in man. The few such studies available # suggest that for normal persons the continued ingestion of fluoride in the recommended concentration of 1 part per 1,000,000 parts of drinking water might lead to the storage of 2 or 3 gm. in a lifetime. It seems highly unlikely that this is a harmful amount; however, more studies, particularly of groups of persons over long periods of time, are needed to finally substantiate the harmlessness of water fluoridation. In cattle ingesting water and food with high fluoride content, stiffness of joints, lameness, and exostoses have been observed.[88] A good many compounds have been proposed for fluoridation of water supplies, but the present evidence indicates that of all these sodium fluoride seems to be the simplest, least expensive, and potentially least harmful.[89]

Several studies in cities in various parts of the world, including not only the United States, Great Britain, and the Scandinavian countries but also Greece and Hungary, strongly suggest that although fluoride is important in reducing dental caries, it is certainly not the only factor. For example, the caries incidence in Hungary is much lower than in regions in the United States where a similarly low fluoride content of the water is found.[90]

With the increasing addition of fluoride to water, the fluoride content of foods must be considered as another source of this element. This is particularly pertinent with respect to certain baby foods, which because of added bone meal may have a relatively high fluoride content.[91]

IRON

The binding of iron by a specific plasma beta-1-globulin is now an established fact both in vitro and in vivo and, in fact, has been proposed as the method of iron transport in the body.[92] Wallenius,[93] using radioactive iron, given both orally and intravenously, found that all of it was bound to the beta-1-globulin—none to other plasma proteins. This seems to establish the normal transport of iron by this so-called iron-binding protein; however, it was found that under certain abnormal circumstances iron could be bound to other plasma proteins, especially albumin.

References 86 and 87.

Most acute infections lead to hypoferremia [94] which is refractory to oral or intravenous iron therapy, the administered iron being found largely in the liver and spleen. The adrenal cortex appears to be involved in the hypoferremia produced in animals by such "stress" situations as fracture of the femur, turpentine abscess formation, and exposure to formaldehyde.[95] That is, hypoferremia regularly occurred after administration of these substances, but when turpentine was given to adrenalectomized animals the hypoferremia was less in degree unless adrenocortical extracts were administered. Likewise, Palmer [96] believes that he can explain the lower serum iron in women than in men by the influence of sex hormones rather than by menstruation. On the other hand, testosterone and progesterone administration do not influence the serum iron concentration.

Interest continues in the intravenous administration of iron preparations. The use of colloidal ferric hydroxide combined with sucrose (saccharated iron oxide) is now well established.[97] Other preparations have included a high-molecular-weight carbohydrate compound with iron (ferric).[98] These products are certainly much less toxic than the older iron preparations; in fact, they are virtually free from side-reactions. Nevertheless, they must be used with caution and only when there is an important indication for their use, because iron so administered is retained in the body and may lead, if too much is given, to structural changes in organs, such as in hemosiderosis or hemochromatosis. Poisoning from oral iron in large quantities given by mistake to children is reported to produce severe gastritis, often with hemorrhage, and striking rises in the serum iron concentration.[99]

The normal adult male has iron stores of between 1,200 and 1,500 mg., repeated bleedings have shown.[100] Once iron stores are depleted they appear to be rebuilt slowly, whether the source of iron is food or it is given as a medication. Greatly increased iron stores have been shown to occur in patients with hemochromatosis and also in some relatives of patients with this disease. The serum iron concentration is usually elevated in patients with infectious hepatitis [101] but does not appear to be directly related to the serum bilirubin. In contrast, patients with cirrhosis of the liver usually have a depressed serum iron concentration.[102]

It is well known that infants over six months of age, if maintained on milk alone, may develop an iron deficiency anemia. They do, however, seem to have adequate iron supplies for the first six months, indicating that iron stores seem sufficient for this period of life.*

COPPER

Copper is necessary for normal hemoglobin synthesis, at least in certain species.[106] Loss of hair, decreased wool production, and the greying of hair have been found in certain animal species on diets deficient in copper. In this connection it should be noted that copper forms an essential part of the enzyme tyrosinase, which is involved in the formation of melanin from tyrosine. Another copper-containing enzyme is ascorbic acid oxidase. Human diets are rarely, if ever, deficient in copper, and so it seems unlikely that copper deficiency is related to greying of the hair in man, and, because of its chronic toxicity, copper should certainly not be adminis-

* References 103-105.

tered except as it occurs in food or as a trace element in iron medication, when the latter is needed.[107] There are between 100 and 150 mg. of copper in the adult human body, the highest concentrations being in the liver and the nervous system.

The copper content of human milk is in the neighborhood of 55 γ per 100 ml.[108] This is a good deal higher than that of cow's milk (nearer 5 to 10 γ per 100 ml.). The figure for human milk more closely approaches the National Research Council's recommended dietary allowances than does that of cow's milk. One should consider copper deficiency as a possible cause of anemia in infants who have been artificially fed, although such anemias have not yet been documented.

The copper content of plasma, red blood cells, and whole blood has been analyzed by improved methods [109] in normal persons, during pregnancy, and in patients with various diseases.† A number of interesting variations have been observed. Hypocupremia is usually found in chronic infections, occurs with many neoplasms, and is striking in Wilson's disease. However, in this condition there is marked increase of copper content of the brain, especially in certain of the basal nuclei. Copper is present in the blood in two fractions. The major portion is bound to a blue protein, ceruloplasmin. Another fraction of serum copper, much smaller in amount, appears not to be bound tightly to protein. There is evidence to suggest that ceruloplasmin does not actively transport copper in the blood but that this function is cared for by the "free" copper, which is not bound to this blue protein. The marked reduction in serum copper in Wilson's disease is paralleled by a low ceruloplasmin concentration.[112] This has led to the speculation that the deposition of copper in the basal ganglia of these patients represents a deficient carrying capacity for copper in the blood. Whether this is the case or not must await further elucidation of the role of ceruloplasmin in copper transport.

COBALT

Vitamin B_{12} contains cobalt as an essential part of its molecule. The administration of cobalt to normal persons or patients with certain kinds of anemia will lead to polycythemia in the first instance and regression of the anemia, as a rule, in the other. Little doubt seems to exist at present that the cobalt-deficiency syndrome in sheep, characterized by severe anemia and weight loss, is due to a deficiency in the synthesis of vitamin B_{12} by these animals.‡ Responses in cobalt-deficient animals to both cobalt and vitamin B_{12} seem similar, if not identical. Further discussion of vitamin B_{12} will be found in the section on vitamins.

ZINC

The role of zinc in metabolism is little known. However, Hock and Vallee § have found considerably larger quantities of zinc in leucocytes than in the serum from which they were drawn. Moreover, these authors have found proteins in the leucocytes which contain zinc. Their exact significance is not known yet. Serum zinc levels have been repeatedly investigated, and, although there is considerable variation in the results from different laboratories, an amount between 100 and 300 γ per 100 ml. would include most of the variations in normal persons.‖ There

† References 110 and 111.
‡ References 113 and 114.
§ References 115 and 116.
‖ References 117 and 118.

is evidence that serum zinc is somewhat reduced in most acute infections.¶ It is not altered in hypochromic (iron deficiency) anemia, but it is low in pernicious anemia in relapse, rising dramatically during the first week after therapy with liver extract.# Zinc is essential for growth of experimental animals; it appears to be related to insulin storage and activity and is an active part of the enzyme carbonic-anhydrase. Zinc disappears quite rapidly from plasma when injected intravenously as the radioactive isotope,[119] especially in patients with certain neoplastic diseases.[120]

¶ References 117 and 118.

References 117 and 118.

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Case Reports

EDEMA AND HYPOPROTEINEMIA FOLLOWING DIARRHEA ASSOCIATED WITH OXYTETRACYCLINE THERAPY

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A CASE of an unusual syndrome of transient edema and hypoproteinemia has been observed. A 28-year-old man developed a syndrome of hypoproteinemia and edema after a period of anorexia and diarrhea subsequent to oxytetracycline (Terramycin) administration. The hypoproteinemia was manifested chiefly by depression of the serum albumin fraction. After spontaneous diuresis and cessation of the diarrhea, the serum protein value rose from an initial level of 2.7 gm. to 6.3 gm. per 100 cc., seven weeks after the onset of the edema. Results of studies of renal, hepatic, and circulatory function were normal. The mechanism of the hypoproteinemia in this case, as in similar reported cases, is not known.

REPORT OF A CASE

L. C., a 28-year-old white single gardener, was admitted to the hospital on Jan. 25, 1952, because of diarrhea of six days' duration. He was perfectly well until 24 days prior to admission, when he noted diffuse headache, swelling of the right side of the neck, and pain on turning his neck to the right. He was seen by a physician, who prescribed phenobarbital. He returned to work the following day and felt well until a week later, when he began to experience general malaise, nausea, and mild diffuse abdominal aching and vomited once. His urine appeared "dark," but stools did not change in color. He felt better after remaining in bed for one day, and he returned to work, only to have recurrence of the latter symptoms and the onset of anorexia. One week prior to entry, he was again seen by his physician, who prescribed oxytetracycline, 0.5 gm. every six hours. After ingestion of a total of 16 capsules of oxytetracycline, the patient developed diarrhea, which progressively increased over a few days up to 8 to 10 loose watery stools per day. Within a few days after the onset of the diarrhea, he noted swelling and stiffness of his hands and swelling of his face and eyes, which was worse on arising in the morning. The nausea and vomiting subsided, but the anorexia persisted until admission. On the day of entry he was still having several soft brown stools daily. There was a 5 lb. (2.25 kg.) weight loss during the week prior to entry.

His mother has diabetes. Four siblings are living and well. His father died accidentally at age 40.

The patient had eczema in childhood. He was in the Philippines and Japan from 1944 to 1946, during which time he was hospitalized for one month because of fungus infection of his feet.

Physical examination disclosed a well-nourished muscular man who was 5 ft. 6 in. (168 cm.) tall and who weighed 151 lb. (68 kg.). The temperature, pulse rate, and respirations were normal. The blood pressure was 134/72. There was moderate edema of both hands, forearms, and lower legs. The skin was clear. Eyes, ears, nose, and throat were normal. There were small, 0.5 to 1.0 cm., soft lymph nodes in the posterior cervical triangles, both axillae, and both inguinal areas. The lungs were clear to percussion and auscultation. The heart was not enlarged;

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no murmurs were heard; there was normal sinus rhythm. The abdomen was not tender to palpation, and no organs or masses were palpable. The genitalia were normal. Rectal examination was negative. Neurological examination was normal.

Examination of the blood disclosed a hemoglobin level of 14.4 gm. per 100 cc., with a hematocrit reading of 46% and a white cell count of 8,050 per cubic millimeter, with a normal differential count. The erythrocyte sedimentation rate was 1 mm. in an hour. Results of initial urinalysis were normal, with a specific gravity of 1.014. Results of 16 subsequent urinalyses were normal except for a slight trace of albumin on the 6th and 13th hospital days, with a specific gravity as high as 1.022 after 14 hours of thirsting. Phenolsulfonphthalein excretion was 25% of the injected dose at 15 minutes, with a total of 57% at 2 hours. On the fourth hospital day the nonprotein nitrogen was 30 mg. per 100 cc.; the CO_2 was 19.8 mEq. per liter; the serum chloride was 107 mEq. per liter; the serum sodium was 147 mEq. per liter, and the serum potassium was 5.6 mEq. per liter. The total serum protein was 2.7 gm. per 100 cc., with a negative formol-gel test. Examination of a stool for occult blood was negative, as was a stool culture for pathogens. There was no growth in three urine cultures. The heterophile agglutination test was negative. The serum bilirubin was 0.5 mg. per 100 cc.; the cephalin-flocculation test was negative; the serum cholesterol was 240 mg. per 100 cc., and the sulfobromophthalein (Bromsulfalein) excretion was normal, with 1% of the injected dye remaining in the serum after 45

Serum Proteins in a Case of Hypoproteinemia

Date	Serum Proteins, Gm./100 Cc.		
	Total	Albumin	Globulin
1/28	2.7	....	....
1/29	3.2	....	....
1/30	3.85	1.94	1.91
2/11	5.21	2.87	2.34
3/ 5	5.91	3.61	2.30
3/18	6.29	4.03	2.26
7/ 1	7.02	4.48	2.54

minutes. The venous pressure on the fifth hospital day was 80 mm. of water; the dehydrocholic acid, N. F. (Decholin) circulation time from arm to tongue was 14 seconds. An electrocardiogram was normal.

X-ray studies of the chest were normal; an intravenous pyelogram was normal; studies of the stomach and small bowel after the ingestion of a barium meal were normal.

The patient was afebrile throughout his hospital stay. He enjoyed a regular diet and was given elixir of camphorated opium tincture (paregoric) during the first few days for relief of mild lower abdominal cramps associated with bowel movements. His stools were soft and bulky and did not have a strong fecal odor; the number of stools gradually decreased from eight on the day of entry to one daily after the 11th hospital day. There were no other complaints. Diuresis began spontaneously on the fourth hospital day and continued for 12 days, with a resulting weight loss of 13 lb. (5.8 kg.) and clearing of all edema. Daily blood pressure determinations were normal. The serial serum protein values are depicted in the Table. On the 16th hospital day the patient was discharged from the hospital. Follow-up examination one month and four months after discharge revealed no abnormalities. He was not seen further and was reported to have been killed in an automobile accident in July, 1953.

COMMENT

This patient presented a diagnostic problem. Initially he was thought to have either acute glomerulonephritis without proteinuria, nephrosis, or a sensitivity type of reaction. Acute glomerulonephritis was not substantiated by the clinical course or the laboratory findings. The syndrome of "acute glomerulonephritis without proteinuria or nonprotein nitrogen retention" * was considered, but in such

* References 1 and 2.

cases one usually finds some other typical manifestations of acute nephritis, such as hypertension or hematuria. The diagnosis of nephrosis was felt to be untenable in the absence of proteinuria of a degree greater than a slight trace on two occasions. It was postulated that a sensitivity type of reaction causing diffuse capillary injury could have accounted for protein transfer to the interstitial fluid, with resulting hypoproteinemia and edema. Proof for such a course of events in this case was lacking.

Peters [3] has shown that albumin depletion in the course of an infectious disease can be connected almost invariably with associated malnutrition. The studies of Balint and Balint [4] of blood protein and fractions thereof in a variety of acute febrile illnesses revealed no statistical difference compared to the sera of normal persons.

In the present case, anorexia, vomiting, and diarrhea no doubt contributed to acute malnutrition. Elman and co-workers [5] have reported as much as 29% fall in the concentration of serum albumin fraction in five dogs on protein- and fat-deficient diets for three weeks. The observed hypoalbuminemia began with the onset of the experiment and was progressive; the authors felt that this indicated "the absence of any store of reserve protein for the manufacture of serum albumin during a dietary induced deficiency." The degree of hypoalbuminemia in this case, the acuity of its apparent onset, and the rapidity of the repletion suggest that, as well as diminished production, there was increased destruction, as in the patient studied by Albright and co-workers.[6] It is impossible to determine from the available data which mechanism played the major role in the patient reported in this paper.

What relation, if any, does this case have to the poorly defined group of idiopathic hypoproteinemias? In none of the seven cases reported in adults† was there a clinical picture comparable to that of this case. Holten's case [11] was that of a 16-year-old youth who had hypoproteinemia after a period of diarrhea. The hypoproteinemia persisted for seven weeks after the stools became normal and was relieved by a transfusion of normal human serum; the globulin fraction was particularly low, with only modest reduction in the albumin fraction. The serum transfusion caused a rise in serum protein greater than could be accounted for by the amount of protein in the serum given.

What part, if any, was played by oxytetracycline administration in the production of the syndrome in this case? Diarrhea following the use of oxytetracycline and other antibiotics is well known. To our knowledge, there have been no reported cases of hypoproteinemia as a sequence to such diarrhea in man or animals. Gabuzda [13] has demonstrated chlortetracycline (Aureomycin) or oxytetracycline given by mouth to malnourished patients may produce negative nitrogen balance, as indicated by increased urinary nitrogen excretion.

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RED CELL APLASIA

Report of a Case and Review of the Literature

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THERE are rare cases in the literature characterized by a severe refractory normochromic normocytic anemia in which there is no reduction in the numbers of leucocytes or platelets. A critical review of these cases of "red cell anemia" shows that in some there are considerable numbers of primitive red cell forms in the bone marrow; these probably represent a maturation arrest of erythropoiesis at an early level. In other cases the bone marrow is characterized by almost complete absence of red cell precursors; these are properly considered cases of true red cell aplasia. The distinction is made clear in the Figure, modified from Whitby and Britton.[1]

In both types of red cell anemia the aspirated bone marrow appears cellular. In the cases of true red cell aplasia the cellularity is due to normal granulopoiesis and megakaryopoiesis, while in those due to maturation arrest the cellularity is due, in addition, to large numbers of primitive red cells. In "aplastic anemia" in the usual sense the bone marrow is acellular.

In the present paper I wish to discuss pure red cell anemia of the aplastic type. I have been able to distinguish from the literature, under such designations as chronic congenital aregenerative anemia, aregeneratory anemia, aleukia hemorrhagica, hypoplastic and aplastic anemia, primary refractory anemia, erythroblastopenia, and red cell anemia, only nine well-documented and four probable examples of this condition. I wish to add an additional case to these, briefly review the literature, and discuss the clinical and hematological features of this condition.

REVIEW OF PUBLISHED CASES

CASE 1 (Kaznelson*).—A 58-year-old man. Hb, 12%; WBC, 4,980; platelets, 207,000. Bone marrow (autopsy): "No nucleated red cells. Neutrophiles, eosinophiles, myelocytes, and megakaryocytes appeared normal."

CASE 2 (Smith†).—A 17-month-old boy. Onset of the anemia was dated to the newborn period "with the clinical and hematological features of a mild type of erythroblastosis." Representative cell counts showed Hb, 8.0 gm.; RBC, 3,700,000; platelets, 390,000; WBC, 19,450. Bone marrow: 0.1% nucleated red cells. Repeated examinations of the bone marrow "have consistently revealed an absence of erythropoiesis without alteration in the granulocyte and platelet elements." Well at age 6½ years with transfusions.

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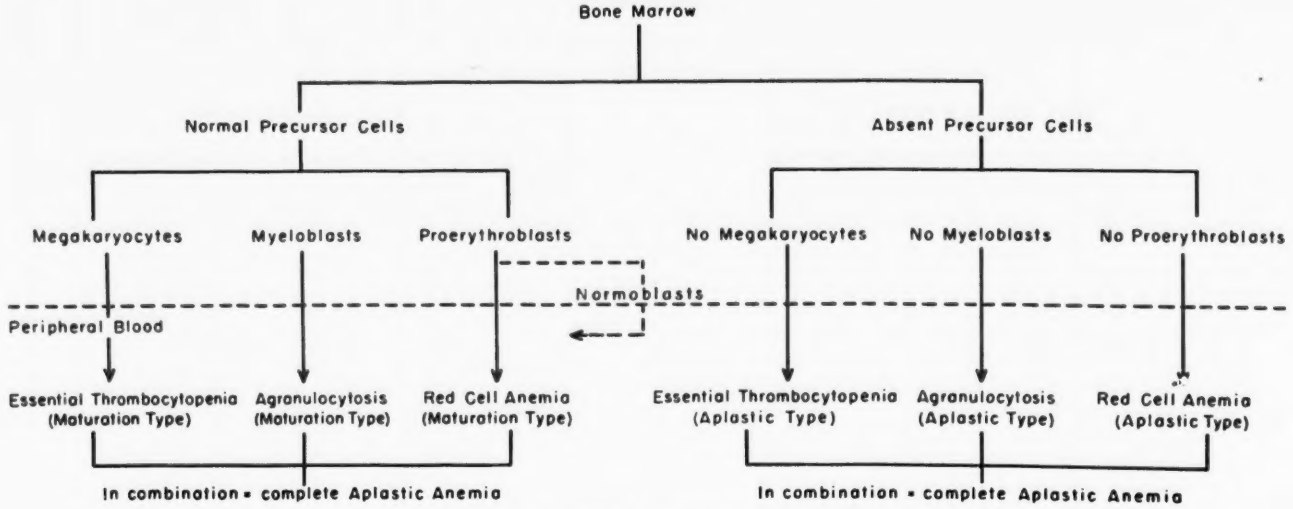
Dr. Marion F. Beard, Director of the Division of Hematology, gave advice and criticism in the preparation of this paper.

* Cited by Lescher and Hubble.[15]

† References 2-4.



Aplastic anemia (modified from Whitby and Britton [1]).

CASE 3 (Kohlbry [5]).—One-day-old girl. Hb, 15%; RBC, 1,900,000; WBC, 6,000 to 15,000; platelets, 150,000 to 300,000. Peripheral blood showed 8 to 14% eosinophiles. "Bone marrow was quite cellular, most of the cells being neutrophilic myelocytes with eosinophilic myelocytes more numerous than usual. Megakaryocytes were present in the normal numbers. Other than for evidence of decreased erythropoietic activity, there was no evidence of an aplastic state." Maintained on transfusions. Age 8 months at writing.

CASE 4 (Macfarlane and Currie [6]).—A 22-year-old woman complaining of weakness, swelling of ankles, breathlessness. Hb less than 20%; RBC, 950,000; WBC, 8,000; platelets, 280,000. Bone marrow showed "aplasia of the erythron; a few scattered macro-normoblasts were seen. The myelogram was otherwise normal." Patient died of a fatal pyrexia following her second transfusion.

CASE 5 (Anderson [7]).—A 2-month-old boy presenting with pallor, vomiting, general irritability, anorexia. Hb, 3.0 gm.; RBC, 610,000; WBC, 7,550; platelets "appeared normal on film." Bone marrow revealed normal cellularity. "The predominate cell is the mature small lymphocyte. Granulocytes are present in all stages and their development appears normal. Megakaryocytes are present in normal numbers. Eosinophiles appear to be in increased proportions while the reticulum cells appear to be normal. The striking feature is the virtual absence of primitive red cells. No proerythroblasts or normoblasts can be found." Three months later was alive and well, receiving frequent transfusions. (I have had the opportunity of seeing the bone marrow films on this patient and have been impressed with the similarity to my own case.)

CASE 6 (Foy and Kondi [8]).—A 46-year-old man complaining of pains all over the body, breathlessness, severe palpitation, and headache of nine weeks' duration. Hb, 2.3 gm.; RBC, 1,300,000; WBC, 5,650; platelets, 700,000. The bone marrow was cellular. Red cell precursors were almost absent. Megakaryocytes appeared normal. There was an increase in eosinophiles (8%) and reticulum cells (2%). Patient had a complete achlorhydria after histamine stimulation. Well eight months after treatment.

CASE 7 (Donnelly [9]).—An 11-week-old boy presenting with pallor. Hb, 16%; RBC, 630,000; WBC, 5,850. Red cells showed macrocytosis, anisocytosis, and poikilocytosis. Platelet count not given. Bone marrow showed "moderate cellularity, red cell precursors almost entirely absent, an occasional normoblast (less than 0.5%), and no gross abnormality of white cells. Apparently a pure red cell aplasia." Sixteen months later the patient was happy and well although requiring frequent transfusions.

CASE 8 (Aldridge and Kidd [10]).—A 13-week-old boy. Blood count showed Hb, 2.52 gm.; RBC, 610,000; WBC, 4,000. Red cells showed anisocytosis, poikilocytosis, macrocytosis, and occasional normoblasts. No bone marrow examination was done at that time. Patient was given transfusions. At age 6 months Hb, 6.3 gm.; RBC, 2,100,000; WBC, 18,900. Reticulocytes, 1%. Bone marrow showed "an extremely cellular marrow with marked myeloid hyperplasia. Red cell precursors were virtually absent. Two further examinations of bone marrow have shown a complete absence of red cell precursors in a cellular myeloid marrow." Child was well at age 10 months, receiving frequent transfusions. (No platelet counts or description of megakaryocytes were given.)

CASE 9 (Smith [4]).—A 1-month-old girl, with Hb 37% and RBC 2,340,000. Repeated bone marrow examinations showed depression of erythropoiesis, with a normal number of granulocytic and platelet elements. Had nephrectomy age 2 months for small cystic kidney. Representative cell count: Hb, 7.0 gm.; RBC, 2,400,000; platelets, 300,000; WBC, 12,100. Bone marrow has shown from 0 to 0.5% nucleated red cells, 0 to 1.5% eosinophiles and 0 to 15% "hematogones" with normal myeloid and megakaryocytic series. Five and one-half years later the patient was living and well, still requiring frequent transfusions.

In addition to the nine cases listed above I have found the following four in the literature, which seem to be examples of red cell aplasia but in which the data as presented leave some room for doubt. Whether such a narrow separation is justified remains to be proved.

CASE 10 (Vogel, Erf, and Rosenthal [11]).—These authors mention under the name of "chronic congenital aregenerative anemia" the case of a 4-year-old boy who developed anemia shortly after birth. Peripheral blood revealed a "decrease in red cells and hemoglobin" and an eosinophilia. Bone marrow showed an increase in eosinophiles and 24% "hematogones." No further data are recorded.

CASE 11 (Vogel and Bassen [12]).—A 2-year-old boy with eosinophilia and low hemoglobin level and few red cells in the peripheral blood, who showed only 5% erythroid elements, 7.6% eosinophiles, and 21% "hematogones" in the bone marrow. No further data are recorded.

CASE 12 (Robson and Sweeney [13]).—A 1½-year-old boy, pale since birth. Hb, 20%; RBC, 1,200,000; WBC, 12,200; platelets, 206,000 to 236,000. Bone marrow showed "remarkable absence of red cell precursors. Erythroblastic hypoplasia almost amounting to an aplasia." The child required frequent transfusions. (No statement is made as to cellularity of the marrow or to the presence of proerythroblasts. It did show 8 to 10% normoblasts and might possibly represent a maturation arrest.)

CASE 13 (Palmen and Vahlquist [14]).—A 2½-month-old girl, pale from birth, found to have a hemoglobin level of 36% and a large spleen at age 6 months. Splenectomy was performed at age 1½ years. The anemia has been distinctly macrocytic from the second year of life. The leucocytes were at first normal in number; however, later they were somewhat reduced, to around 3,000 with a normal differential count. Platelets varied from 290,000 to 560,000. Bone marrow: "The specimen is moderately rich in cells. It shows a relative increase of leucopoiesis with a normal differential picture, but a decrease of erythropoiesis with, however, a normal maturation. The megakaryocytes and reticulum cells are normal." Patient has required no transfusions since age 3 years. At age 10 hemoglobin has stabilized between 55 and 60%. (In addition, these authors describe three other patients, in all of whom the leucocytes were even lower (1,600 to 3,200) and in two of whom the bone marrow was "poor in cells").

Numerous other cases ‡ described as "red cell anemia" or "hypoplastic anemia" have failed to meet the criteria of normal granulopoiesis and megakaryopoiesis with virtual absence of red cell precursors in the bone marrow. Most of these are actually cases of maturation arrest of erythropoiesis. I have been unable to obtain the original papers of Moeschlin and Rohr § or of Gasser.‖

REPORT OF A CASE

A 51-year-old white male mine worker consulted his local physician in January, 1949, with the complaint of weakness. He was found to be anemic and was treated with blood transfusions and liver and iron injections. This therapy was continued for a period of six months, after which he was referred to a hematologist for a consultant opinion. He had recently been given a transfusion, and so his blood cell count at that time was recorded as red blood cells, 4,200,000 per cubic millimeter; hemoglobin, 11.2 gm., and white blood cells, 14,000 per cubic millimeter, the differential white cell count showing 84% polymorphonuclear leucocytes, 10% lymphocytes, and 6% monocytes. Physical examination was essentially negative. Urinalysis, gastric analysis, and roentgenological examination of the gastrointestinal tract were all normal. Bone marrow aspiration was reported as showing "active hemopoiesis, with many large macrocytes and no cells suggestive of neoplasm of leukemia. There was considerable variation in the size and shape of the red cells. Polymorphonuclear cells (segmented) were 21%; lymphocytes, 2%; eosinophilic promyelocytes, 6%; stab cells, 15%; myelocytes, 15%; juvenile forms, 16%; myeloblasts, 2%; normoblasts, 20%; blasts, 1%; monocytes, 1% and megaloblasts, 1%."

‡ Baar, H., cited by Lescher and Hubble [15]; Lupu and Nicolan, cited by Lescher and Hubble [15]; Kark, R. M., cited by Robson and Sweeney,[13] and References 15-27.

§ Cited by Smith.[4]

‖ References 28 and 29.

During the ensuing month the patient was given transfusions and was given folic acid as well as liver and iron. By the end of this time, however, the red cell count had fallen to 2,800,000 and hemoglobin, to 8.5 gm., but the white cell count was still 12,300, with a normal differential count.

Transfusions were continued, and he was given a variety of treatments, including iron, liver, folic acid, crystalline vitamin B_{12}, and cobalt and iron.

In January, 1951, two years after the patient first consulted his local physician, a bone marrow examination was normal except for 37% eosinophilic polymorphonuclear leucocytes. There were 22% normoblasts. A further bone marrow examination, three months later, was again reported as normal except for 18% eosinophiles. There were 24% normoblasts. None of these bone marrow preparations are available to us for study. In June, 1951, a bone marrow examination by a second hematologist reported the absence of normoblasts from the differential count. The count was as follows: 10% eosinophiles, 18% lymphocytes, 26% myelocytes, 20% metamyelocytes, 24% polymorphonuclear neutrophiles, and 2% phagocytic cells. No normoblasts were seen.

The patient continued to receive blood transfusions and various combinations of the above therapies until May, 1952, approximately three and one-half years after he first consulted a doctor. He then voluntarily omitted transfusions because he was asymptomatic. His physician told him at that time that his blood cell count was normal. In July, 1953, he suffered a fractured femur. Routine hospital admission blood cell count was normal, in spite of no transfusions for over 12 months. One month later it was noticed that he was again becoming anemic, and he was again given transfusions several times between August and December, 1953.

When first seen by me, in December, 1953, his peripheral blood cell count showed red blood cells, 2,600,000; hemoglobin, 7.2 gm.; reticulocytes, 0.1%; packed cell volume, 21%; mean corpuscular volume, 81 cu. μ; mean corpuscular hemoglobin, 27.8 $\mu\gamma$; mean corpuscular hemoglobin concentration, 34.2%. The white cell count was 14,000. Differential count showed 54% neutrophilic polymorphonuclear leucocytes, 38% lymphocytes, 3% monocytes, 4% eosinophilic leucocytes, and 1% basophiles. The platelet count (Dameshek method) was 500,000 per cubic millimeter. The stained blood films appeared normal.

Apart from a bluish gray hue of the skin, probably a manifestation of hemosiderosis, physical examination showed no abnormalities. Bone marrow was aspirated from the sternum. Fragments were cellular, and there were many cells in the fragment trails. Megakaryocytes were plentiful. Granulopoiesis appeared normal. The outstanding feature was the complete absence of erythroid precursors. Differential count showed the following: polymorphonuclear neutrophiles, 34%; band cells, 22%; myelocytes, 14%; promyelocytes, 8%; myeloblasts, 5%; eosinophiles, 5%; lymphocytes, 8%, and reticulum cells, 4%.

One month later the peripheral blood and bone marrow pictures were essentially unchanged, except that the bone marrow at this time showed 19% eosinophiles. Again, there was a complete absence of erythropoiesis.

The patient's condition has remained unchanged over the past three months. I have aimed to keep his red cell count about 2,500,000 by transfusions. When the count falls below this figure he does not feel well and is unable to get about. The patient continues to complain of weakness, but he is able to lead a life of restricted activity in a fairly satisfactory manner.

COMMENT

Etiology.—No etiology is known, and quite probably different factors are responsible in various cases. None of the usual chemical or physical agents, such as benzene, heavy metals, irradiation, etc., have yet been definitely incriminated. Gasser [28] describes 10 children with complete temporary disappearance of normoblasts in the bone marrow following infection or toxic or allergic influences, a condition somewhat analagous to the "aplastic crisis" of congenital hemolytic anemia. Smith [4] believes pure red cell aplasia in infancy to be a congenital anomaly, on the same basis as other congenital anomalies, and cites a case associated with cystic kidney (Case 8) and another (Case 7) associated with a high titer of anti-A antibodies

in the mother. He believes that cases with retarded onset, such as those in adults and older children, may represent a more chronic form of the transitory acute erythroblastopenia described by Gasser. Certainly, many of the cases, including the present one, mention bone marrow eosinophilia as being prominent, suggesting allergic or noxious influences as a factor. The spontaneous remission lasting more than a year in this case, may also be partially explained on such a basis, although I was unable to single out any one chemical or physical agent as being suspect, except that the remission did cease coincidental with physical trauma.

Congenital inborn errors of metabolism have frequently been referred to, but there is little evidence to support this.[24]

Cathie,[25] in his cases of maturation arrest anemia ("erythrogenesis inperfecta"), mentions two patients who originally had fairly plentiful red cell precursors but whose bone marrows "now appear to be approaching exhaustion." This suggests that prolonged maturation arrest may in some cases precede a true aplasia. That this might be the situation in my case is suggested by the previous bone marrow reports of 20 to 24% normoblasts in the face of marked anemia, although no hypoplasia was reported. This contraction of hemopoietic tissue may also result from the depressing effects of frequent transfusions, as suggested by Smith.[4]

Nordenson [30] feels that from a functional point of view the three systems of blood formation, myelopoiesis, erythropoiesis, and thrombocytopoiesis, are to be regarded as a uniform organ and that isolated changes cannot, as a rule, exist for any length of time without other systems being affected. There is, however, a small group of cases in which the aplasia seems to be limited to the erythron, and separation of these cases should aid in the study of their pathogenesis.

Age, Sex, and Distribution.—The majority of cases have been recorded in infants and very young children, but the age range has been from 1 day to 58 years. There appears to be no sex predilection or limit in geographic distribution.

Symptomatology.—Symptoms have for the most part been exclusively those of anemia—pallor, breathlessness, palpitation, tachycardia, headache, faintness, easy fatigability, irritability, restlessness, anorexia, and musculoskeletal aches and pains. Edema and hemic murmurs are occasionally noted. Conspicuous is the absence of purpura or bleeding phenomena. Infection seems no commoner in these patients than in general, and their resistance to infection does not seem to be impaired. Lymphadenopathy and enlargement of the liver and spleen are absent until after numerous transfusions.

Blood Changes.—As a rule the red cell count and hemoglobin level are quite low when the patient is first seen, and frequently the red cell count is less than 1,000,000 per cubic millimeter. On stained film the red cells are usually normochromic and normocytic, although anisocytosis, poikilocytosis, and macrocytosis have all been described. Adequate platelets are noted on smear, and platelet counts are within normal limits. Leucocytes are normal or slightly elevated. Bleeding and coagulation times are normal, and clot retraction is good. Red cell fragility is normal, and there is no evidence of increased blood destruction found in the plasma, urine, or stools. The red cell survival time (method of Ashby) was normal in my patient.

Bone Marrow.—The bone marrow is cellular, and if infection is present myeloid hyperplasia may be found. Megakaryocytes are present in normal proportions. The

striking finding is an almost complete absence of proerythroblasts and normoblasts, these cells composing usually less than 0.5% of the nucleated marrow cells. The presence of increased numbers of eosinophiles and of eosinophilic myelocytes and of reticulum cells has been frequently noted. Smith,¶ Vogel, Erf, and Rosenthal,[11] and Vogel and Bassen [12] have commented upon the presence of large numbers of primitive cells termed "hematogones" and closely resembling ordinary lymphocytes in size and morphology. I have been unable to recognize these cells either by supravital techniques or Jenner-Giemsa stains in my case or by stained films in the bone marrow from Anderson's case.

Treatment.—Pentnucleotide, iron, iron and cobalt, iron and copper, bone marrow extract, splenic extract, high protein and high vitamin diets, vitamin C, folic acid, and vitamin B_{12} have all been used without apparent effect. The serum vitamin B_{12} concentration in my patient was normal (160 $\mu\gamma$ per milliliter) by the method of Ross.[31] I can find no true instances in which splenectomy has been of benefit. This is to be expected, as there is no evidence of increased blood destruction. Smith's [4] two patients showed no response to corticotropin (ACTH) and cortisone.

Foy and Kondi [8] report an amazing response to riboflavin. In their case riboflavin administration was followed in seven days by the appearance of reticulocytes in the peripheral blood, reaching a maximum of 27% on the 12th day of therapy. The red cell count and hemoglobin level doubled in 21 days, and the patient remains well 8 months after cessation of therapy. He was on no other medication at this time and would appear to have had a specific reticulocyte response. On the basis of this report, I gave adequate riboflavin therapy both orally and parenterally to my patient, without improvement.

Prognosis.—Most of the published cases have had short follow-ups, although several have been of five or six years' duration. It would appear that with frequent transfusions these patients can be maintained for long periods of time, although they are quite apt to develop hemosiderosis. My case and perhaps others # would seem to indicate that spontaneous remissions can occur, although spontaneous "cure" is doubtful.

SUMMARY

An attempt has been made to separate those cases of anemia due to absence of precursor cells in the bone marrow from thoses due to maturation arrest and the more general aplastic and hypoplastic states. I have been able to find at least nine such cases in the literature, to which I have added another. The literature is briefly reviewed.

Etiology, age, sex, geographic distribution, symptomatology, blood changes, bone marrow findings, and treatment are discussed.

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ELASTICA DISEASE

Case of Grönblad-Strandberg Syndrome with Gastrointestinal Hemorrhage

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PSEUDOXANTHOMA elasticum is a well-known disease, described and named by Darier in 1896.* When associated with retinal alterations (angioid streaks, etc.), the complex is known as the Grönblad-Strandberg syndrome. The disease is presumed to be due, basically, to elastic tissue degeneration. Cutaneous lesions vary from pinhead- to pea-sized yellowish flat papules that often fuse to form plaques. The symmetrical distribution is in flexural folds (axillae, antecubital fossae, inguinal regions), the sides of the neck, upper and inner aspects of the thighs, and over the abdomen. In extreme cases there is obvious loss of cutaneous elasticity. The unilateral or bilateral retinal changes, accompanied by loss of visual acuity, appear to be due to degenerative changes of the elastica of Bruch's membrane. The disease may be found at any age in both sexes, but most commonly it begins in childhood or early adult life. A familial history, fairly regularly elicited, emphasizes the role of inheritance in this basic deficiency of elastica.

Since Darier established this disease as an entity, observations have been made by a number of authors that have indicated the fact that visceral involvement by this process should be expected. Though clinical reports of this involvement are many, there have only been four such case reports with anatomic observations of visceral alterations. Of these, only one received the benefit of microscopic study of the encountered vascular lesions. The patient presented, therefore, represents the second report of microscopic visceral vascular lesions in this disease. This became possible when a partial gastrectomy was performed for uncontrolled gastric hemorrhage in a patient who was subsequently proved to have the Grönblad-Strandberg syndrome.

REPORT OF A CASE

A 23-year-old white woman was admitted to Wadsworth Hospital on March 28, 1953, one-half hour after vomiting a quart (0.95 liter) of bright red blood. The patient first had gastrointestinal difficulty at the age of 18, when she had an episode of massive hematemesis that necessitated nine blood transfusions. She was placed on an ulcer regimen, and three months later a roentgen study of the gastrointestinal tract showed evidence of duodenal scarring. She did not adhere to the ulcer regimen and had occasional episodes of abdominal pain. In 1952, at an Army hospital, roentgen study of the gastrointestinal tract was reported as negative. Two or three days prior to admission the patient noted the onset of "stomach cramps." The patient had

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* Reference 1, cited by Carlborg.[9]

had some impairment of vision in the right eye that began after a blow to the head at the age of 18. Unusual skin and retinal lesions had been noted at one time during her military service, though information as to their nature was not available. No history of a familial trait was elicited.

Physical examination revealed a well-nourished pale white woman. Her blood pressure was 90/60. Her pulse rate was 80 per minute, and her temperature was 97 F. Plaques of flat yellowish papules were seen on the flexor surfaces of the arms, in the axillae, in the groin, and on the sides of the neck. There were gray-brown retinal streaks on both fundi and a small brown patch in the upper outer quadrant of the right retina. The remainder of the examination was negative except for an appendectomy scar and minimal lower abdominal tenderness.

Laboratory Data.—The blood hemoglobin was 9.9 gm. per 100 cc.; the hematocrit reading was 29%. Guaiac test of the stool was negative for occult blood, and the bleeding-clotting times were normal.

Course in Hospital.—The patient was given blood, carboxymethylcellulose (Carmethose), and atropine. The blood pressure stabilized at 96/60. After 1,500 cc. of blood was given, the hemoglobin rose to 11.2 gm. and the hematocrit level rose to 33%. In the evening of the day of admission the patient had a large emesis of red blood. She was given another 1,500 cc. of blood. The following day the patient had an emesis of 1,000 cc. of blood and her blood pressure fell to 50/30. Because of the continued bleeding a partial gastric resection was performed. No definite bleeding site could be demonstrated in the stomach or duodenum. The patient had a difficult postoperative course, but there was no recurrence of bleeding. She improved rapidly and was discharged on May 15, 1953. At that time her hemoglobin was 17.3 gm. She was eating well and gaining weight.

Pathology.—Biopsy of a specimen taken from the antecubital skin revealed the characteristic proliferation and nodular degeneration of elastica fibers described in this disease. Swelling, granularity, fragmentation, and loss of tinctorial quality was associated with crumbling and eventual disappearance of the elastic fibers in these foci. The fixed tissue response, beyond homogenization of collagen in such zones, was insignificant.

The subtotally resected stomach revealed only superficial mucosal hemorrhages and erosions. Capillaries and veins of mucosa and submucosa were widely dilated. The small and medium caliber arteries of the gastric wall and adjacent gastrocolic and gastrohepatic ligaments exhibited a selective degenerative change of their elastica, especially the internal elastic lamella. These changes were similar to those of the skin, with certain exceptions. Intimal, oftentimes obliterative, sclerosis, with and without mural fibrosis and calcified plaque formation, was frequently found. Tortuous, fusiform, and symmetrically "bead"-shaped microaneurysms were often encountered in such arteries as well. These changes did not involve all arteries. No arterial ruptures and no foci of gastric infarction could be demonstrated. Further histopathologic details of this case and other related cases will be published later by one of the authors (L. K.).

COMMENT

Several authors have suggested the probable systemic nature of the disease, not only by virtue of ocular and skin changes occurring simultaneously but because of such regularly recurring phenomena as signs of visceral, cerebral, and peripheral arterial disease; hemorrhagic diathesis from the nose, gastrointestinal tract, gums, uterus, genitourinary tract, and skin, and a distinct increase in the incidence of thyrotoxicosis and diabetes mellitus.†

Since 1901 only 10 case reports of gastrointestinal hemorrhage occurring simultaneously with pseudoxanthoma elasticum, with or without angioid streaks, have been published (Table). Five of these were females and five were males. The average age for this group was slightly under 32. However, the average onset of gastrointestinal hemorrhage occurred at 26 years of age. In three of the four fatal cases the patients apparently succumbed because of these enteric epi-

† References 2-11. References 4 and 8 are cited by Carlborg.[9]

sodes of bleeding, although in one instance, reported by Carlborg, the hemorrhage appeared to be due to rupture of esophageal varices. The remaining two reports establish no mechanism for the loss of blood, and in only one, by Prick, is there mention of a specific alteration in the mesenteric vessels. Whether the bleeding can be directly or indirectly attributed to these degenerative changes of vascular elastica remains to be established. In the present case report, although we have extended knowledge of the vascular alterations, the gastric specimen did not demonstrate the mechanism of hemorrhage either. It may well be that the residual portion of gastric wall holds the secret to this.

It is hoped that this report will stimulate clinicians who study such patients to establish the presence or absence of vascular disease peripherally and viscerally.

Pseudoxanthoma Elasticum, With or Without Angioid Streaks in Retina, Associated With Gastrointestinal Hemorrhage

Year	Author	Age, Yr.	Sex	Observation *	Anatomic Findings	
					Gross	Microscopic (Viscera)
1901	von Tannenhain	48	F	N	Gastric scar; enteric hemorrhage	None recorded
1938	Law	17	M	L, N	Dilated submucosal veins; mucosal hemorrhages, acute mucosal ulcer (laparotomy); postoperative gastrojejunostomy with peritonitis	None recorded
1938	Prick	48	F	N	Aortic and cerebral artery sclerosis	Elastica degeneration in coronary, renal, pancreatic, uterine, cutaneous, and mesenteric arteries; central and hepatic veins of liver; trabeculae of spleen
1944	Carlborg	20	M	C	.....	None recorded
		32	F	C	.....	.....
		?	M	N	Cirrhosis, liver, with ruptured esophageal varices	None recorded
		52	F	C	.....	.....
1948	Revell; Carey	31	M	C	.....	.....
		29	F	C	.....	.....
1952	Wolff, Stokes, and Schlesinger	9	M	C	.....	.....

* C, clinical; L, laparotomy; N, necropsy.

It will, we hope, urge anatomic pathologists to survey specimens and necropsies in such patients for the gaps in knowledge that must certainly exist, not alone within the confines of the cardiovascular system but in all areas where elastica is an integral part of the supporting connective tissue stroma.

SUMMARY AND CONCLUSIONS

The clinical association of pseudoxanthoma elasticum, the Grönblad-Strandberg syndrome, and gastrointestinal hemorrhage is reemphasized.

The second report of microanatomic alterations of the vascular structures of the enteric canal is presented.

The degenerative changes of skin, eye, and viscera reported by others, and demonstrated in this case report, unquestionably demonstrate that this syndrome appears to involve the elastica primarily.

Gastrointestinal hemorrhage in young people without clinical or roentgen evidence of varicosities or ulcerative disease should suggest a careful search for elastica alterations of enteric vasculature.

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SYSTEMIC BLASTOMYCOSIS TREATED WITH 2-HYDROXYSTILBAMIDINE

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CHICAGO

SCHOENBACH and his co-workers first reported the successful treatment of North American blastomycosis with stilbamidine in 1951.[1] Prior to that time experiences with the toxic effects of stilbamidine had been well documented.* In 1948, Snapper described the effect of 2-hydroxystilbamidine on the course of multiple myeloma. Of particular interest was the lessened toxicity of the 2-hydroxy form of the drug.[7] Snapper and others,† in later work, confirmed this decreased toxicity and later reported the effectiveness of this form of stilbamidine in the treatment of blastomycosis.[10] We would like to add another case of systemic blastomycosis with apparent cure following intensive treatment with 2-hydroxystilbamidine.

REPORT OF A CASE

R. D. M., a 41-year-old white locomotive engineer, was admitted to the dermatologic and medical service at Michael Reese Hospital on April 8, 1953, with a known diagnosis of disseminated blastomycosis. The past history revealed that in 1927 he had lived in Sault Sainte Marie, Mich. While there he spent 32 days fighting a forest fire, with severe exposure to smoke. However, no known illness resulted. For the next three or four years he served in the Merchant Marine on various cargo vessels, none of which carried livestock. He later held odd jobs, such as being a commercial fisherman and working on road gangs. For approximately the past 20 or 21 years he has worked as switch engine engineer for one of the local steel companies, during which time physical check-ups were done every three months, including chest x-rays. His were normal at all times.

In April, 1952, while visiting his parents, in Sault Sainte Marie, he developed an illness diagnosed as influenza. This was associated with a cough. The only unusual activity participated in was deer hunting. He ate deer meat, rabbits, and Northern pike while on this trip. Upon returning to Chicago he entered another hospital, where a right middle lobe lobectomy was performed for a presumed bronchogenic carcinoma. Prior to the surgery the patient had complained of progressively severe cough and hemoptysis of two months' duration. Preoperative workup, which included bronchoscopic studies, revealed a right lower lobe infiltrate of rapidly increasing size, the nature of which could not be determined clinically.

The following is the histological summary of tissues removed surgically: Histologic preparations from many levels of these lung tissues were examined. The solid portions have a large amount of chronic granulation tissue, in some portions with marked infiltrations of lymphocytes and plasma cells and in some portions with marked infiltrations by polymorphonuclear leucocytes, but there are also lesions in the form of tubercles or tubercle-like structures. The centers of these have dense leucocytic exudates; the marginal portions, epithelioid cells, with several multinucleated giant cells. In some respects these lesions resemble tubercles. A search in the giant cells

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* References 2-6.

† References 8-10.

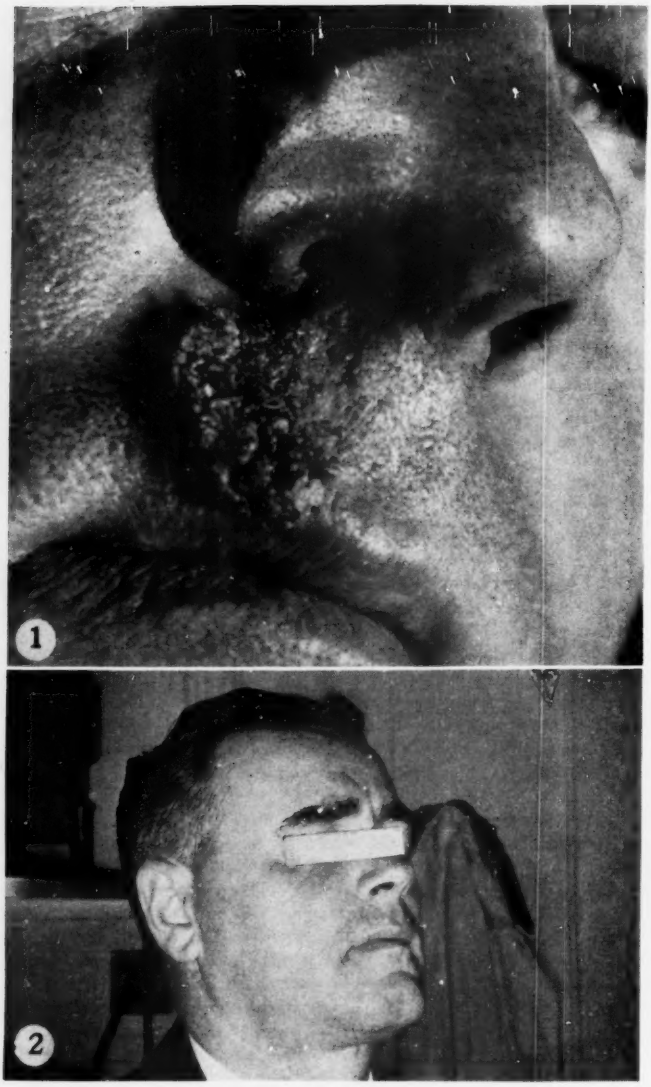

Fig 1.—Lesion of blastomycosis.
Fig. 2.—Appearance of the upper lip six months after termination of therapy.

and also in the leucocytic exudates in the center of the tubercles demonstrates the presence of yeast organisms, some of them in budding stages. The lung parenchyma is not uniformly involved but has various stages of the exudative inflammation.

Immediately following surgery, blastomycetes were found in the sputum and treatment with undecylenic acid was instituted. One month later, while the patient was still on treatment, the sputum had cleared but cutaneous lesions appeared on both elbows, the chin, and the upper lip. The lesions rapidly increased in size, and x-ray therapy was begun, with disappearance after 10 treatments of all the skin lesions but the one on the upper lip, which had progressed to involve the ala nasi and nostril on the right side. Further treatment with arsphenamine and chlortetracycline (Aureomycin) had no effect on this lesion. The patient was told at this time that there was evidence of the disease in the left lower lobe of his lung.

After this course of treatment the patient was seen by one of us, A. B., who confirmed the diagnosis by identification of Blastomyces dermatitidis in the biopsy of the lip lesion, and the patient was admitted to Michael Reese Hospital for further study. Results of laboratory studies, including complete blood cell count, erythrocyte sedimentation rate, urinalysis, sputum examination and culture, liver- and renal-function studies, and an electrocardiogram were all within normal limits. Skin testing for blastomycosis, actinomycosis, coccidioidomycosis, and histoplasmosis yielded negative results. The tuberculin test with purified protein derivative (PPD), 1st strength, was positive. An x-ray survey revealed lytic bone lesions involving the right third rib anteriorly and the superior portion of the right tibia. During the delay entailed in obtaining a supply of 2-hydroxystilbamidine, treatment was begun with stilbamidine. The patient received 150 mg. of stilbamidine in an intravenous drip of 200 cc. of 5% dextrose in water for two consecutive days, for a total of 300 mg. of this form of the drug. On the third day, and for 26 consecutive days thereafter, 225 mg. of 2-hydroxystilbamidine‡ in the same diluent was administered intravenously daily, for a total of 5,850 mg. of the drug. During the administration of the fluid, the flask was covered with a layer of aluminum foil to protect it from the light. The patient was instructed to remain in his darkened room throughout the day but was permitted in the hospital corridors and bathroom at night. Hepatic and renal function was studied at weekly intervals and remained within normal limits throughout the course of treatment. Following the first several infusions a transient malar flush appeared. Local phlebitis was troublesome at the site of the intravenous injections. This was eliminated by the use of hot compresses for three hours daily after the infusion was completed.

The crusted lesion on the upper lip is seen in Figure 1. At the completion of therapy, the large crust had dropped off, leaving a smaller area of granulation tissue. The patient was discharged from the hospital on May 21, 1953. At the time of discharge he felt well and returned immediately to his old job. He was seen a month later, at which time the initial skin lesion on the lip had practically disappeared. X-rays taken on Aug. 26, 1953, revealed complete disappearance of the rib lesions and an 85% decrease in the size of the lesion of the right tibia. Figure 2 is the appearance of the upper lip in November, 1953, six months after the termination of therapy. At that time there was no evidence of systemic or local recurrence of the infection. For the first time, however, he complained of sensations of numbness over the bridge of his nose, cheeks, eyelids, and forehead of three or four weeks' duration. Examination disclosed no objective evidence of sensory disturbance.

The patient was last seen in March, 1954, when x-rays of the right leg revealed complete healing of the lesion in the tibia. Clinically he was quite well, with no signs of recurrence, and the sensations of numbness were rapidly disappearing.

COMMENT

The above case represents another apparent cure of systemic blastomycosis treated with 2-hydroxystilbamidine, although the follow-up period of 11 months is still too short for a definitive conclusion. No true toxic effects were noted during therapy with 2-hydroxystilbamidine. The results with the massive dosage used—close to 6 gm.—agree with the superior results Snapper and associates [10] obtained with larger doses. It seems apparent that the drug is nontoxic for normal liver and

‡ The Wm. S. Merrell Company, Cincinnati, supplied the 2-hydroxystilbamidine.

kidneys, but it may be contraindicated when there is evidence of preexisting liver or renal disease. The numbness complained of by this patient probably represents an atypical type of neuropathy due to the stilbamidine used in the first two days of therapy. Others § have observed this under identical conditions and report a mild, delayed type of trigeminal neuropathy when one or two doses of stilbamidine have been used and followed by 2-hydroxystilbamidine. This has not been observed when 2-hydroxystilbamidine has been used alone.

SUMMARY

An apparent cure of systemic blastomycosis following treatment with a massive dose of 2-hydroxystilbamidine is reported. No evidence of recurrence has been observed in an 11-month follow-up period. A mild, delayed type of trigeminal neuropathy developed after six months, but this apparently resulted from the two doses of stilbamidine used at the onset of therapy.

§ Personal communication to the authors from Dr. Kushner, associate of Dr. Snapper.

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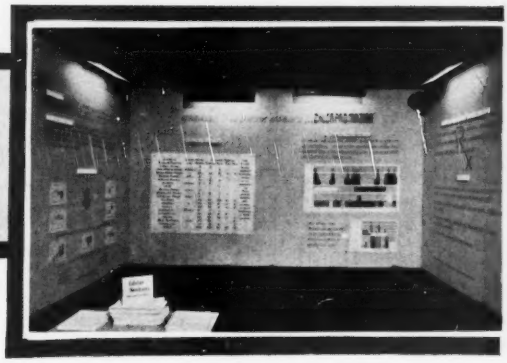
Scientific Exhibits



OBSERVATIONS ON AN EFFECTIVE ANTIEMETIC—CHLORPROMAZINE

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CHLORPROMAZINE (10-[γ - dimethylaminopropyl] - 2 - chlorophenothiazine hydrochloride) is a new drug that effectively protects dogs from apomorphine-induced emesis and motion sickness.* It acts by depressing the emetic chemoreceptor trigger zone and the vomiting reflex site within the central nervous system.[3] Laboratory toxicity studies indicated that chlorpromazine is relatively safe for use in man.[4] Therefore, we undertook a further evaluation of hemodynamic and toxicological effects in dogs and in man. These are briefly summarized in Figure 2.

Upon completion of the hemodynamic and toxicity studies, an effort was made to evaluate the clinical effectiveness of chlorpromazine as an antiemetic. These observations are briefly summarized in Figures 3 to 5. The chlorpromazine was administered to patients with persistent vomiting who had failed to respond to commonly employed antiemetic measures and had become definite therapeutic problems. In each patient, the cause of nausea and vomiting has been reasonably well established before starting chlorpromazine therapy, because its use may mask a serious pathological condition. Therapeutic efficacy was graded as excellent when vomiting was stopped and nausea completely relieved; as good when vomiting was stopped, but slight nausea persisted; as fair when vomiting stopped, but nausea continued; as poor when neither vomiting nor nausea were relieved.

Dosage and Route of Administration.—Patients were given 10, 25, or 50 mg. doses of chlorpromazine, orally or intramuscularly, depending on the status of the patient and severity of his symptoms. The usual effective dose is 25 mg. orally;

From Baylor University College of Medicine and Jefferson Davis Hospital.

Shown as a scientific exhibit of the Section on Experimental Medicine and Therapeutics at the 103rd Annual Meeting of the American Medical Association, San Francisco, June 21-25, 1954.

* References 1 and 2.

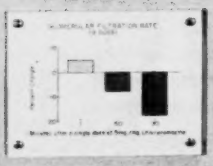
VOMITING IS FREQUENTLY A SERIOUS THERAPEUTIC PROBLEM. MANY COMPOUNDS HAVE BEEN USED FOR TREATMENT OF NAUSEA AND VOMITING, BUT UNTIL RECENTLY NONE HAVE BEEN CONSISTENTLY SATISFACTORY.

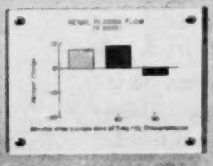
CHLORPROMAZINE APPEARS TO BE AN EFFECTIVE ANTI-EMETIC AGENT. IN EXPERIMENTAL ANIMALS THIS COMPOUND HAS BEEN SHOWN TO ACT SPECIFICALLY ON THE CENTRAL NERVOUS SYSTEM, DEPRESSING THE VOMITING REFLEX, THUS INHIBITING APOMORPHINE INDUCED NAUSEA AND VOMITING IN NEARLY ALL OBSERVATIONS.

PHARMACOLOGY

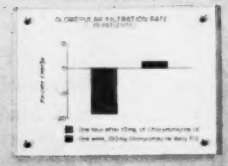
DOG

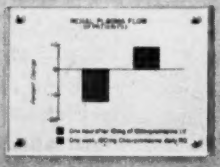
HUMAN



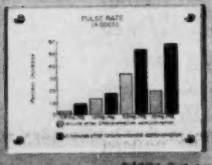


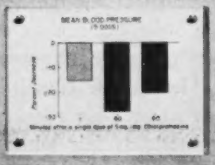
RENAL FUNCTION

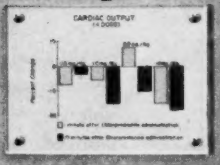




CARDIOVASCULAR EFFECTS IN DOGS







HUMAN TOXICITY STUDIES WHICH HAVE PROVEN NEGATIVE

SERUM BILIRUBIN
THYMOL TURBIDITY
SULFOBROMOPHTHALEIN
URINE ANALYSIS
HEMATOCRIT
ERYTHROCYTE COUNT
LEUCOCYTE COUNT
DIFFERENTIAL COUNT
ELECTROCARDIOGRAPHIC CHANGES

OBSERVATIONS OF ...CHLORPROMAZINE

however, ambulatory patients should be started on 10 mg. orally and the dose gradually increased, so that it controls symptoms without causing drowsiness and other side-effects.

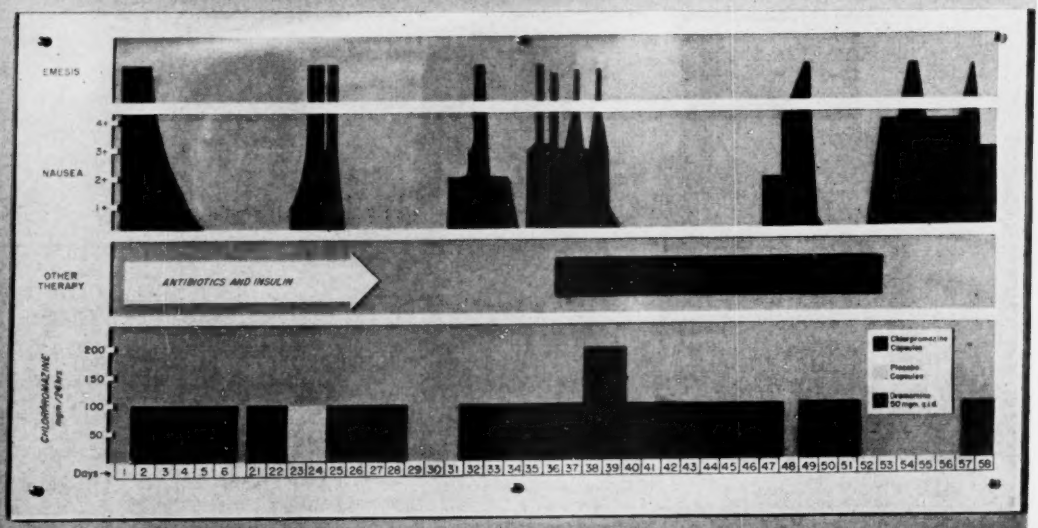
Patients who were unable to retain oral doses long enough for adequate drug absorption, because of vomiting, were first given the drug intramuscularly. Once vomiting was controlled, the patients were continued on oral medication. It is advisable to keep patients in bed to offset any hypotensive effects that may result during initial therapy. And, because chlorpromazine augments the action of barbiturates,

CLINICAL RESULTS

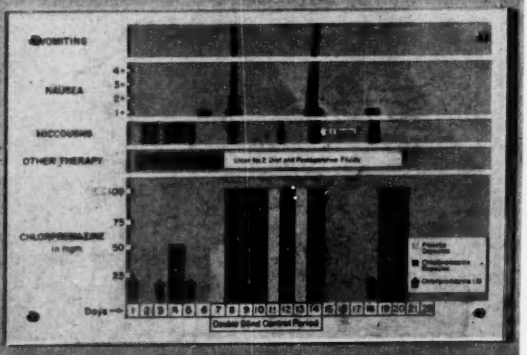
Etiology of Nausea and Vomiting	Average Days	Number Patients	Therapeutic Response Excellent	Good	Fair	Poor	Side Effects
Digitalis Therapy		6	6				Varying
Hexamethonium Therapy	15.6 days	3		3			degrees of
Nitrogen Mustard Therapy		38	24	8	4	2	drowsiness;
Urethane Therapy	with	2	1		1		common
Antibiotic Therapy		10	6	4			but not
Narcotics	extremes	6	6				incapacitat-
LK 51		1		1			ing.
Quinidine Therapy	of from	2		1		1	Some
Aminophyllin Therapy		6	4	1	1		postural
Aminopyrine Therapy	6 days	1		1			dizziness
Sub-Totals		75	47	19	6	3	and
Infections	to	45	36	6	1	2	dryness
Toxicosis		49	34	9	4	2	of mouth.
Cardiovascular	25 days	8	7	1			Slight drop
Gastrointestinal		32	24	3	4	1	in blood
Pregnancy		78	55	14	5	4	pressure
Spinal Anesthesia	1 dose	30	28			2	
Miscellaneous		19	12	5		2	
TOTALS		338	243	57	20	16	

A TYPICAL CASE STUDY

THE PATIENT WAS IN DIABETIC ACIDOSIS COMPLICATED BY HEPATITIS AND BACTEREMIA. HE HAD SEVERE VOMITING AND NAUSEA WHICH RESPONDED WELL TO CHLORPROMAZINE; EVEN IN INSTANCES WHERE OTHER ANTI-EMETIC AGENTS FAILED.


EMESIS
NAUSEA
4+
3+
2+
1+
OTHER THERAPY
ANTIBIOTICS AND INSULIN
CHLORPROMAZINE mgm./24 hrs.
200
150
100
50
Days →
1 2 3 4 5 6 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58
Chlorpromazine Capsules
Placebo Capsules
Suppositories 50 mgm. q.i.d.

THIS PATIENT HAD INTRACTABLE HICCOUGHS, WHICH WERE ARRESTED WITH SINGLE DOSES OF CHLORPROMAZINE.



opiates, and other central nervous system depressants, the usual dose of these drugs should be reduced when they are used in combination with chlorpromazine.

Side-Effects.—Sedation was the most prominent side-effect from chlorpromazine. Although its incidence was 47%, the sedation, in most cases, was mild and did not appreciably interfere with the patient's normal activity. Dryness of the mouth

DOSAGE AND METHOD OF ADMINISTRATION

FOR ROUTINE USE OF CHLORPROMAZINE A DOSE OF 25 MGM. SHOULD BE USED. DRUG BECOMES LESS EFFECTIVE WHEN DOSE IS DROPPED MUCH BELOW 25 MGM. ADMINISTERED EITHER ORALLY OR INTRAMUSCULARLY.

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SUMMARY

CHLORPROMAZINE IS AN EFFECTIVE AGENT FOR BLOCKING THE MECHANISM OF NAUSEA AND VOMITING WITHOUT PRODUCING PROHIBITIVE SIDE EFFECTS.

NO EVIDENCE TO INDICATE ANY DANGEROUS UNTOWARD EFFECTS IN DOSES LESS THAN 50 MGM.

INITIAL DOSES FREQUENTLY ASSOCIATED WITH DIZZINESS AND MAY CAUSE ORTHOSTATIC HYPOTENSION.

PREFERABLY USED FOR NON-AMBULATORY PATIENTS.

(19%) was another mild side-effect noted, but it seldom bothered the patients. Although dizziness occurred fairly frequently (24%), few patients complained about it. A fall in blood pressure, observed in 12% of the group, was mild in most cases. However, in seven patients blood pressure fell from 30 to 60 mm. Hg after parenteral therapy. In three of these, it fell to 90/60 mm. Hg.

REFERENCES

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2. Cook, L., and Toner, J. J.: The Antiemetic Action of Chlorpromazine, SKF No. 2601-A (RP-4560), abstracted, J. Pharmacol. & Exper. Therap. **110**:12, 1954.

3. Brand, E.; Harris, D.; Borison, H., and Goodman, L. S.: The Antiemetic Activity of 10-(3-Dimethylaminopropyl)-2-chlorphenothiazine (Chlorpromazine) in Dog and Cat, J. Pharmacol. & Exper. Therap. **110**:86, 1954.

4. Courvoisier, S.; Fournel, J.; Ducrot, R.; Kolsky, M., and Koetschet, P.: Pharmacodynamic Properties of Chlorpromazine, Arch. internat. pharmacodyn. et therap. **92**:305, 1953.

News and Comment

ANNOUNCEMENTS

Laboratory Training Refresher Courses.—The Department of Health, Education, and Welfare, of the Public Health Service, announces a schedule of Laboratory Refresher Training Courses at Chamblee, Ga., to be given through the current year up to June, 1955. The courses will include the following subjects:

Laboratory Diagnosis of Bacterial Diseases

8.40—Part 1. General Bacteriology
Sept. 13-24, 1954

8.41—Part 2. General Bacteriology
Sept. 27-Oct. 8, 1954

Laboratory Diagnosis of Parasitic Diseases

8.00—Part 1. Intestinal Parasites
Sept. 13-Oct.8, 1954

8.01—Part 2. Blood Parasites
Oct. 11-29, 1954

Laboratory Diagnosis of Rabies—8.26
Oct. 18-22. 1954

Laboratory Diagnosis of Viral and Rickettsial Diseases—8.20
Oct. 18-29, 1954

Laboratory Diagnosis of Bacterial Diseases

8.50—Enteric Bacteriology
Oct. 18-29, 1954

Laboratory Methods in Medical Mycology

8.15—Part 1. Cutaneous Pathogenic Fungi
Nov. 1-12, 1954

8.16—Part 2. Subcutaneous and Systemic Fungi
Nov. 15-26, 1954

Laboratory Diagnosis of Tuberculosis—8.55
Nov. 15-26, 1954

Laboratory Methods in the Study of Pulmonary Mycoses—8.17
Nov. 29-Dec. 10, 1954

Laboratory Diagnostic Methods in Veterinary Mycology—9.40
Dec. 13-17, 1954

Laboratory Diagnosis of Rabies—8.26
March 14-18, 1955

Laboratory Diagnosis of Viral and Rickettsial Diseases—8.20
March 14-25, 1955

Laboratory Diagnosis of Malaria—8.05*

Virus Isolation and Identification Techniques—8.21*

Laboratory Diagnosis of Influenza—8.25*

Typing of Corynebacterium diphtheriae—8.42*

Special Problems in Enteric Bacteriology—8.51*

Phage Typing of Salmonella typhosa—8.52*

Courses 8.20, 8.21, 8.25, and 8.26 will be presented at the Virus and Rickettsia Laboratories, Montgomery, Ala. Other courses listed will be presented at the laboratories at Chamblee, Ga. Completion of Course 8.15 or equivalent education or experience is a prerequisite for Course 8.16. Courses followed by an asterisk will be presented by special arrangement. The roster of Course 8.20 will close six weeks prior to the beginning of the course.

Information and application blanks should be requested from Laboratory Training Service, Communicable Disease Center, U. S. Public Health Service, P. O. Box 185, Chamblee, Ga.

Course in Practical Electrocardiology.—A course in practical electrocardiology will be presented during the week of Dec. 6 to 10, under the auspices of University of Texas Postgraduate School of Medicine, Baylor University College of Medicine, and the Houston Heart Association. The guest lecturer, Dr. Demetrio Sodi-Pallares, Chief of the Department of Electrocardiology of the National Institute of Cardiology of Mexico City, will lecture each evening during the week from Monday to Friday from 7:30 p. m. to 10:00 p. m. During the daytime hours registrants will be invited to attend the various hospitals in the Medical Center during periods when routine hospital tracings are being read by the hospital electrocardiologists. In addition, registrants in smaller groups will be given individualized instruction in interpretation of specific tracings by various members of the faculty of both schools, who will be in attendance during the sessions.

The course, which includes adult and pediatric electrocardiology, is primarily designed to acquaint general practitioners as well as internists with practical aspects of electrocardiology, with emphasis upon those tracings commonly encountered in practice.

At a later date the details and schedule of the specific subjects to be discussed and the time and place of the various sessions will be announced. Further inquiry and advance registration may be made by telephoning The University of Texas Postgraduate School of Medicine (Telephone: LI-6986).

Columbia University Plans Pharmacy Bicentennial Conference.—Announcement of a special scientific congress, to be held in New York on Oct. 14 and 15, devoted to a review of the present status of research and treatment of critical diseases and to a forecast of future research, has been made by Columbia University's college of pharmacy.

The two-day "Bicentennial Conference," entitled "Pharmacy and the Conquest of Disease," will be dedicated to the major advances made in recent years in the treatment of disease and in public health and to a forecast of future research developments. It is a part of the year-long observance of the bicentennial of the university and a tribute to the hundred twenty-fifth anniversary of the founding of Columbia's college of pharmacy.

Gastroenterological Convention.—The Nineteenth Annual Convention of the National Gastroenterological Association and the First Annual Convention of the American College of Gastroenterology will he held at The Shoreham in Washington, D. C., on Oct. 25, 26, and 27, 1954.

In addition to several interesting individual papers on gastroenterology and allied fields, the program will include a panel discussion on "Twenty-Five Years' Observation of the Gallbladder Controversy," a panel discussion on "Amebiasis" by members of the staff of the National Institutes of Health, Bethesda, Md., and a symposium on "Esophageal Varices."

The Sixth Annual Course in Postgraduate Gastroenterology, under the personal direction of Dr. Owen H. Wangensteen, of Minneapolis, and Dr. I. Snapper, of Brooklyn, will be given on Oct. 28, 29, and 30, 1954, at The Shoreham and Walter Reed Army Hospital. Participating in giving the course will be a distinguished faculty from the various medical schools and the staff of Walter Reed Army Hospital.

The scientific sessions on Oct. 25, 26, and 27 are open to all physicians without charge. The postgraduate course will only be open to those who have matriculated in advance.

Copies of the program and further information concerning the postgraduate course may be obtained by writing to National Gastroenterological Association, 33 West 60th St., New York 23.

American Psychosomatic Society.—The American Psychosomatic Society will hold its Twelfth Annual Meeting at The Claridge Hotel, in Atlantic City, on Wednesday and Thursday, May 4 and 5, 1955. This meeting will be immediately preceded by those of the American Society for Clinical Investigation and the Association of American Physicians. It will be followed by the meeting of the American Psychoanalytic Association.

The Program Committee would like to receive titles and abstracts of papers for consideration for the program no later than Dec. 1, 1954. The time allotted for the reading of each paper will be 20 minutes. The Committee is interested in investigations in the theory and practice of psychosomatic medicine as applied to adults and children in all of the medical specialties and in contributions in psychophysiology and ecology.

Abstracts for the Program Committee's consideration should be submitted in duplicate and should be sent to the Chairman, 551 Madison Ave., New York 22.

LAWRENCE S. KUBIE, M.D.
Chairman, Program Committee
PAUL B. BEESON, M.D.
ROBERT A. CLEGHORN, M.D.
STANLEY COBB, M.D.
WILLIAM J. GRACE, M.D.
GEORGE C. HAM, M.D.
THEODORE LIDZ, M.D.
LOUIS LINN, M.D.
I. ARTHUR MIRSKY, M.D.

Conference on Silicosis.—A conference on silicosis and ocupational chest diseases jointly sponsored by the McIntyre Research Foundation, of Toronto, Canada, and the Saranac Laboratory, Saranac Lake, N. Y., has been arranged for Monday, Tuesday, and Wednesday, Feb. 7, 8, and 9, 1955, in the Town Hall at Saranac Lake. The papers to be presented in the five full sessions will all report on original work conducted or sponsored by either the McIntyre Research Foundation or the Saranac Laboratory. In addition, there will be papers presented by guest lecturers.

Anthony J. Lanza, M.D., formerly director of the Institute of Industrial Medicine and now emeritus professor of Industrial Medicine at New York University-Bellevue Medical Center, has been named chairman of the conference.

The business arrangements, including reservations, will be handled by Norman R. Sturgis, Jr. All communication concerning the conference should be addressed to Mr. Sturgis, Saranac Laboratory, Saranac Lake, N. Y.

Television Symposium on the Management of Hypertension.—On Thursday evening, Sept. 23, 1954, from 6:00 p.m. to 7:00 p.m., Eastern Daylight Saving Time, the American College of Physicians will utilize television through a national closed circuit over the Columbia Broadcasting System to carry to its members and their colleagues a symposium on the management of hypertension, This telecast is made possible through the cooperation and generous support of Wyeth Laboratories, Inc., Philadelphia, and will be the first nationwide closed circuit hookup for postgraduate medical education.

The panel of distinguished physicians who will participate includes Drs. Cyrus C. Sturgis, F. H. Smirk, Garfield G. Duncan, R. W. Wilkins, and Edward D. Freis.

Professor Smirk is one of the topmost authorities of the world on methonium compounds. He went to New Zealand from England in 1940 to take the Chair of Medicine at the University of Otago. He is a Fellow of the Royal College of Physicians of London and of the Royal Australian College of Physicians, being the Senior Censor for the latter in New Zealand. He appears on this program as an official representative of the Royal Australasian College of Physicians in connection with an exchange-guest program being arranged between the two Colleges.

A "closed TV circuit" is one by which reception is controlled and not open to the general TV public. This telecast canot be picked up in the home, but the invited audience must go to the TV receiving station. Twenty-three such receiving stations will be used; these will be

located in Boston; New York; Philadelphia; Washington, D. C.; Pittsburgh; Charlotte, N. C.; Atlanta; Cincinnati; Detroit; Chicago; St. Louis; Milwaukee; Minneapolis; Memphis; Dallas, Texas; Houston, Texas; New Orleans; Denver; Salt Lake City; Los Angeles; San Francisco; Baltimore, and Cleveland.

Nutritional Aspects of Blood Formation.—A Symposium on the Nutritional Aspects of Blood Formation will be held at the University of Cincinnati on Friday, Oct. 22, 1954. This Symposium is being made possible by support from The National Vitamin Foundation and will feature reports and discussions on the stated subject by a selected group of specialists in the field.

The meetings of the Symposium will begin at 9:15 a. m. in the Auditorium, College of Medicine, Eden and Bethesda Avenues, Cincinnati, and will continue through 5:00 p. m. The morning session will be under the chairmanship of Dr. Richard W. Vilter, Associate Professor of Medicine, College of Medicine, University of Cincinnati, and the afternoon session will be under the chairmanship of Dr. M. A. Blankenhorn, Professor of Medicine, University of Cincinnati, and Director of the Department of Internal Medicine, Cincinnati General Hospital.

The Symposium is open to all interested physicians and scientists.

Continuation Course in Infectious Diseases.—The University of Minnesota announces a continuation course in infectious diseases for general physicians which will be held at the Center for Continuation Study next Nov. 18 to 20. Practical and fundamental aspects of the diagnosis and management of infectious diseases of all types will be taken up. Guest speakers will be Dr. Harry Eagle, Chief, Section of Experimental Therapeutics, National Microbiological Institute, National Institutes of Health, Bethesda, Md., and Dr. Ellard M. Yow, Assistant Professor of Medicine, Baylor University School of Medicine, Houston, Texas. Dr. Eagle will also present the annual *Journal-Lancet* Lecture on Thursday evening Nov. 18. The course will be presented under the direction of Dr. W. W. Spink, Professor, Department of Medicine, and members of the faculty of the University of Minnesota Medical School and the Mayo Foundation will complete the faculty. Lodging and meal accommodations are available at the Center for Continuation Study.

Nutritional Aspects of Blood Formation.—A Symposium on Nutritional Aspects of Blood Formation will be presented at the University of Cincinnati College of Medicine, Auditorium, Eden and Bethesda Aves., Cincinnati, Friday, Oct. 22, 1954.

Dr. Richard W. Vilter is in charge of the program. The speakers will include Dr. Carl V. Moore, St. Louis; Dr. George E. Cartwright, Salt Lake City; Dr. J. N. Williams, Madison, Wis., and several others, equally prominent.

SCIENTIFIC EXHIBITS

The A. M. A. ARCHIVES OF INTERNAL MEDICINE is pleased to introduce in this issue a new feature called "Scientific Exhibits."

This feature attempts to preserve in more permanent form some of the instructive Scientific Exhibits that are presented at the Annual Meetings of the American Medical Association. Although thousands of physicians attend the Annual Meetings, viewing and studying the scientific exhibits at first hand, other thousands are unable to attend. For the first time, the latter group is now given the opportunity to see the exhibits reproduced in the pages of the various A. M. A. Specialty Journals.

While it is at present impossible to publish all the Scientific Exhibits presented at each Annual Meeting of the American Medical Association, it is feasible to select a representative few for the purpose of introducing the new feature to the readers of this periodical. Should "Scientific Exhibits" be well received, it is planned to expand the new department in future issues of the A. M. A. ARCHIVES OF INTERNAL MEDICINE.

Books

Atlas of Exfoliative Cytology. By George N. Papanicolaou, M.D., Ph.D. Price, $18.00. Pp. 56, with 36 color plates. Harvard University Press, Cambridge, Mass., 1954.

Although desquamated epithelial cells have been studied for more than a century, their clinical significance has been realized only in recent years. The present widespread clinical use of the cytological approach is due largely to the untiring efforts of Papanicolaou and his associates and to the techniques and applications developed by his laboratory.

The present volume is intended partially to fill the need for publications describing and illustrating the large variety of exfoliated cells. The book limits illustration and discussion to distinct cell types rather than attempting to include all the abnormal cells found in body fluids. There is a detailed chapter on technique and a chapter on the cytologic criteria of malignancy in general. Plates depicting representative cell types from lesions of the female genital tract, urinary and male genital system, respiratory system, digestive system, and breast are discussed in subsequent chapters.

The binding is loose-leaf, so that new material may be added as progress in the field continues. The additional expense of such a volume may be compensated for by the advantage of periodic revision, without the necessity of replacing the present excellent plates.

The value of an atlas of this type depends on the quality of the plates, and the author has to choose between photomicrographs and drawings. Photomicrographs are, of course, more accurate, but in many cases the cell in question is overlapped by surrounding cells or does not all lie in the same plane of focus, so that good reproduction is difficult. Colored drawings may show slight deviation in color, and the artist tends to overemphasize minute details of cell structure at the expense of over-all accuracy. Papanicolaou has solved this problem by an excellent compromise. Twenty-four of the plates are colored drawings by the well-known artist H. Murayama, and 12 plates are photomicrographs in color. The drawings are unusually accurate as well as pleasing to the eye, but the photomicrographs look more like the cells actually do. Under ideal conditions most of the drawings will probably be replaced eventually by the photomicrographs. However, without any modification whatever, the plates in the present Atlas are superior to anything else in the field.

The brief text accompanying the plates is concise and informative.

The value of the study of exfoliative cells is now established, and it remains only for the method to find its exact place in the study of tumors. As Papanicolaou points out, the smear, although a most acceptable diagnostic aid, should not be used to replace biopsy. The smear needs careful, time-consuming study by well-trained personnel. Interpretation must be conservative, and only a conclusively positive smear may be considered as justifying a major operative procedure.

The book is recommended for departments of pathology and others interested in exfoliative cytology.

Peptic Ulcer. By C. F. W. Illingworth, Regius Professor of Surgery, University of Glasgow. Price, $8.50. Pp. 287. E. & S. Livingstone, Ltd., 16 and 17 Teviot Place, Edinburgh 1, 1953.

Peptic ulcer of the stomach and duodenum is an important cause of morbidity and exerts an increasing social and economic effect in our time. A concise readable presentation of the subject, such as is given in this compact treatise, is therefore timely and valuable.

No attempt is made by the author to evaluate or even mention all the literature, which is indeed immense, that bears upon the subject of peptic ulcer. Rather, an attempt has been made to include the more important articles that have appeared through the years, leaving the greater share of the text for an expression of the author's own viewpoint, attained by a lengthy and rich experience with the clinical and surgical aspects of the disease.

The introductory chapters give a concise and understandable introduction to the physiologic, anatomic, and pathologic aspects of the problem. This material is presented in such a way as to be particularly valuable to the general reader, and yet is detailed enough to be rewarding to one with a special interest in the subject.

The author adopts a reasonably conservative approach to the question of treatment, though, as is not surprising, he indicates a preference for early surgical intervention in peptic ulcer both of the duodenum and of the stomach. He is in agreement with the majority opinion of this era, that a well-performed subtotal gastric resection is the operation of choice for duodenal ulcer as well as gastric ulcer, and he cites a very gratifying experience in the employment of this procedure.

Short chapters are devoted to the major complications of peptic ulcer, the ulcer-cancer problem in peptic ulcer of the stomach, and peptic ulcer of the esophagus and Meckel's diverticulum. The importance of the generous use of whole blood in exsanguinating hemorrhage is stressed, as is the wisdom of prompt surgical intervention in instances in which there is no certainty of the cessation of bleeding after 24 or 48 hours of observation.

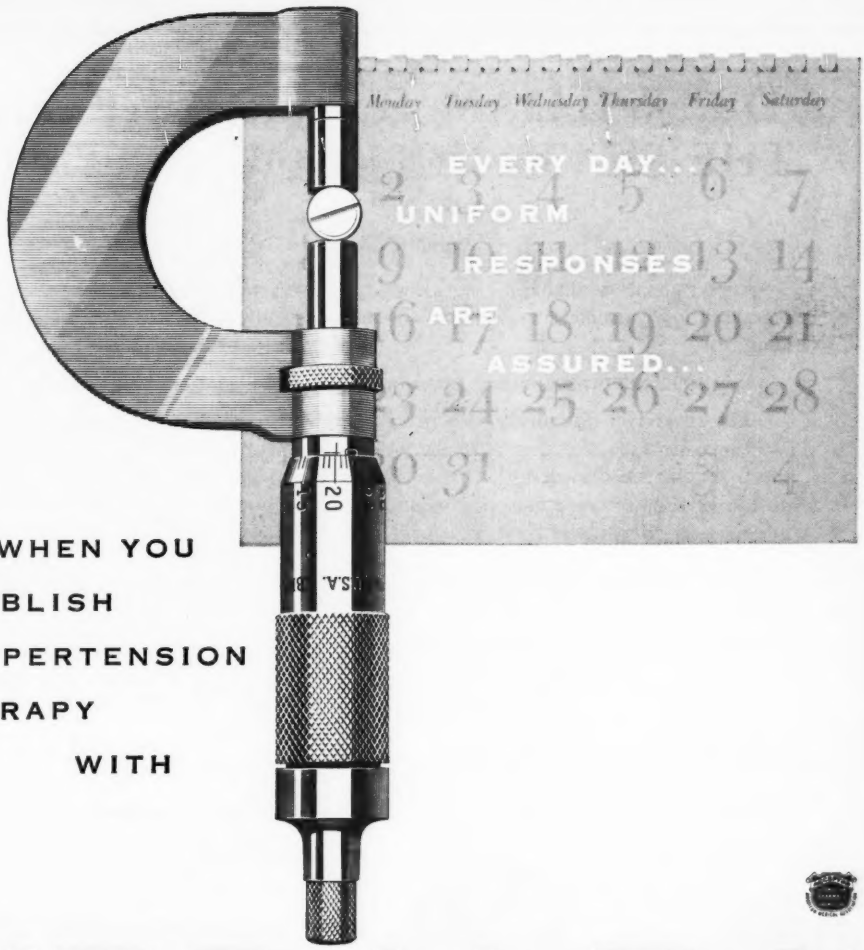
Altogether this book is well written, and it is a pleasure to read it. It presents a concise balanced view of the peptic ulcer problem, and it will make a welcome addition to the library of the general practitioner, as well as to that of the physician or surgeon with a primary interest in gastrointestinal problems.

Understanding the Japanese Mind. By James Clark Moloney, M.D. Price, $3.50. Pp. 252. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1954.

Author Moloney has taken upon himself a monumental task in attempting an assay of the individual and national character of the Japanese. He is a psychoanalyst from Birmingham, Mich., who had visited Japan before the war and came back during the period of occupation, as a lecturer. The author has made an extensive survey of the psychoanalytic, cultural, and historical literature of Japan and has combined this with his own experience and knowledge. Dr. Moloney describes the modification of classical Freudian analysis as it has been syncretized into the Japanese setting.

In his preface he states that "the Japanese are neither mysterious, inscrutible nor unpredictable." This view of the Japanese by Occidentals comes from ignorance of the Oriental culture. The Japanese per se possesses a blurred identity, with multitudinous rigid obligations to the emperor, father, family, and other symbols of authority. From the moment of birth, insensible and unconcious submissiveness is inculcated in the child, destroying his rights of individuality. Even when insane, the individual conforms to authority. A surprising example which the author cites is the use of rice-paper partitions and nonscreened glass windows in one institution where violent patients were housed. Another surprising fact is that there is a comparatively low incidence of psychosis. This can be partially explained by the warm, close relationship of mother and child. The national trait of "copying" is explained by the psychologic principle of identification with the enemy as a means of self-preservation, be it nation or group. Basically, the Oriental can be characterized as being "id-ic" and feminine, as compared to the American character of being "ego-ic" and masculine. This helps in part to shed light on their strong death instincts as a wish to return to the womb. It is therefore the aim of the Japanese analysts to tighten the thongs of conformity in their patients, in contrast to the practice in our culture, where individualism and free expression are encouraged in psychoanalysis.

One becomes frequently aware that perhaps the author is presenting another thesis than his purported one. The ominous fact that the Japanese "manifest destiny" has been instilled in their minds for centuries is disturbing. This book could serve as a guiding light to the Occidental who must pursue his calling in this group of the world's people.



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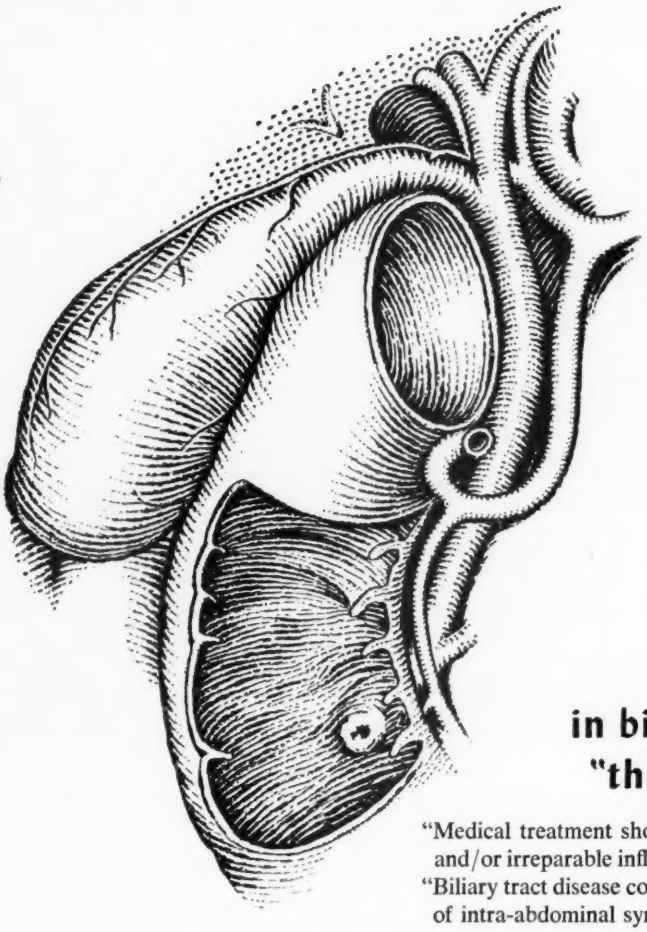

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1. Segal, H.: Postgrad. Med. *13*:81, 1953. 2. O'Brien, G. F., and Schweitzer, I. L.: M. Clin. North America *37*:155, 1953. 3. Beckman, H.: Pharmacology in Clinical Practice, Philadelphia, W. B. Saunders Company, 1952, p. 361.

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References:

1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953. 2. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 3. Plotz, M.: N. Y. State J. Med. *52*:2012 (Aug. 15) 1952.

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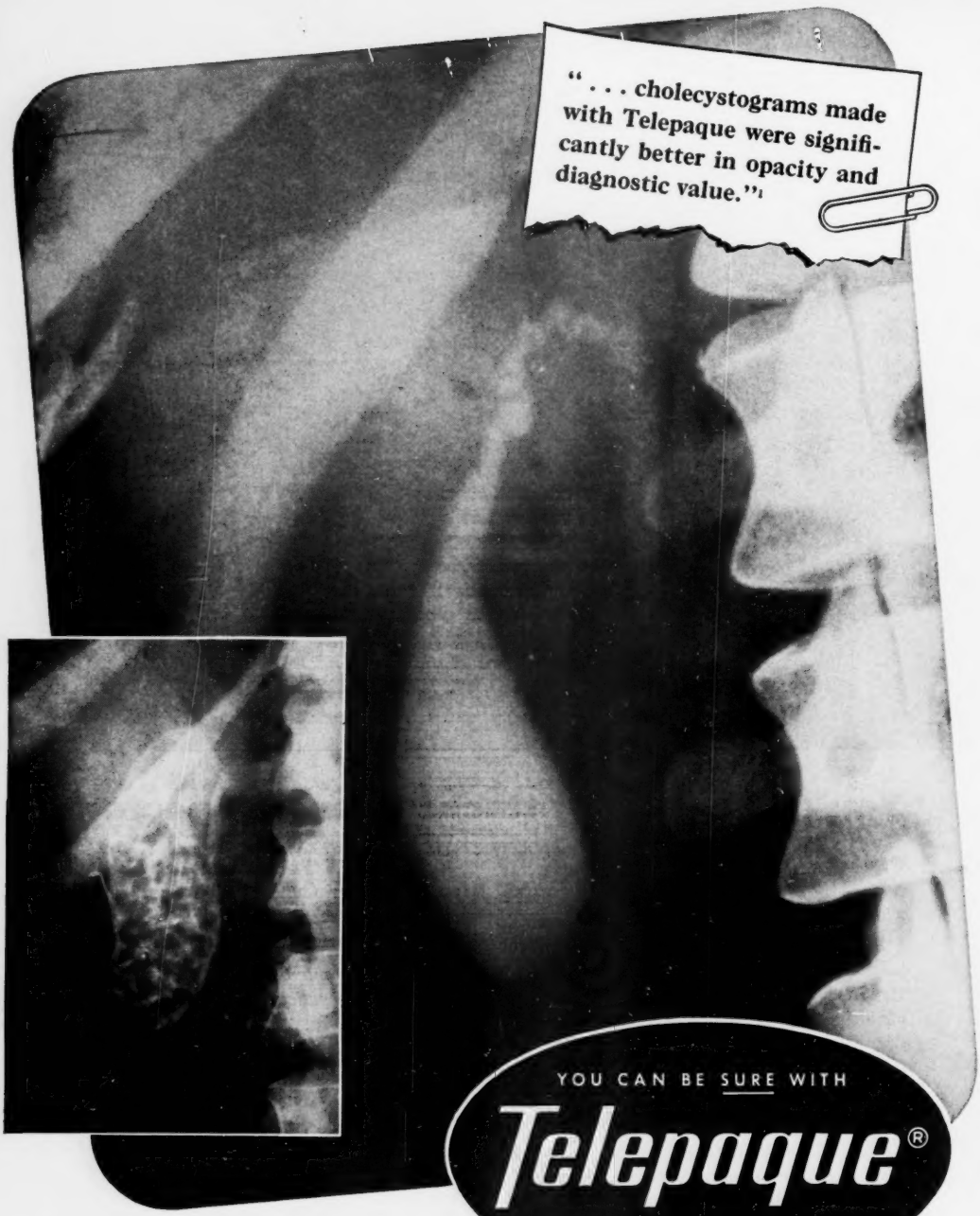

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1 Abel, M.S., Lomhoff, I.I., and Garcia, C.V.: *Permanente Found. Med. Bull.*, 10:95, Aug., 1952.
2 Lowman, R.M., and Stanley, H.W.: *Connecticut Med. Jour.*, 16:591, Aug., 1952

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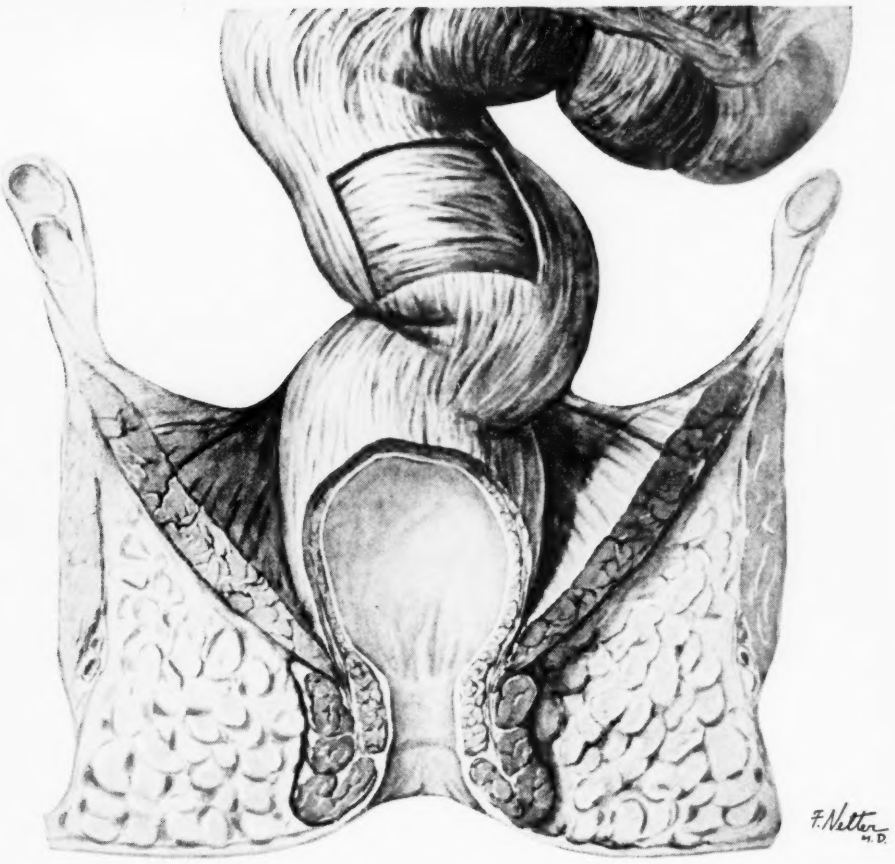

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